Metal-on-metal total hip arthroplasty

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clinical results, metal ions and bone implications

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Golf van Biscaye

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Wat men begapje wol, moat men ek behapje kinne

Wat men bereiken wil moet men ook kunnen overzien

GENERAL INTRODUCTION

Evolutions in hip arthroplasty

Total hip arthroplasty (THA) has evolved as a very successful treatment for alleviating pain and function in end-stage osteoarthritis of the hip. The rate of hip joint replacement surgery is increasing. In 2009 the number of hip replacements grew by 3.4% compared to 2008, and had grown by 26.3% compared to 2003.[1] In the Netherlands a growth of 44% is expected from 1997 to 2020.[2] Initially designed for elderly patients with crippling osteoarthritis, the procedure is now performed in young patients hoping to regain quality of life and physically demanding activities.

In just over 100 years a lot has changed. In the late 19th century, interpositional arthroplasty with fascia lata, skin or even pig's bladder was offered as the first surgical attempt to treat osteoarthritis of the hip. This was followed by a vitallium cup covering the femoral head by Smith-Peterson.[3] Wiles developed the first prosthetic total hip replacement in 1938, using stainless steel components fitted with bolts and screws.[4] In the 1950s McKee and Watson-Farrar introduced their metal-on-metal hip, switching from stainless steel to cobalt-chrome-molybdenum.[5] Ring, Huggler and Müller also designed metal-on-metal arthroplasties in the 1960s.[6]

In the 1970s metal-on-metal implants had virtually disappeared due to the success of Charnley's high-density polyethylene low friction arthroplasty using acrylic bone cement.[7] The concept of cemented polyethylene cups articulating with cemented cobalt-chromium femoral components was also adopted for use in hip resurfacing. This so-called double-cup arthroplasty was simultaneously developed by Wagner, Paltrinieri and Trentani, Freeman, Tanaka, Furuya and Nishio, Gerard, Eicher and Capello and Amstutz, but exhibited poor long-term performance compared with THA.[8]

First generation cemented THAs showed premature loosening associated with localized areas of bone resorption (osteolysis), and this was attributed to so-called cement disease.[9] This gave rise to the development of cementless, press-fit prosthetic components but unfortunately the issue of periprosthetic osteolysis remained. In the late 1970s, polyethylene wear particles rather than cement particles were recognized as the major cause for osteolysis and subsequent aseptic loosening through various macrophage and cytokine interactions.[10] It also became apparent that the large femoral heads used in hip resurfacing led to accelerated polyethylene wear.[8]

So-called alternative bearing materials were developed aiming to limit wear debris, osteolysis and aseptic loosening. These comprise of ceramic-on-ceramic, ceramic-on-modified polyethylene, metal-on-metal, metal-on-modified polyethylene and ceramicised metal-on-modified polyethylene bearings.[1] Modified polyethylene includes polyethylene that has been cross-linked or has the addition of vitamin E. Ceramicised metal includes oxidized zirconium.

AIMS OF THE THESIS

This thesis focuses on one of the alternative bearings above, namely metal-on-metal total hip arthroplasty. General aim of this thesis is **to determine the clinical outcome and bone implications of metal-on-metal total hip arthroplasty.**

Four objectives are distinguished:

1. To determine the mid and long term clinical outcome of cemented 28mm metal-on-metal THA in comparison with metal-on-polyethylene THA;
2. To determine the short term clinical outcome and periprosthetic bone implications of cementless large femoral head metal-on-metal THA in comparison with metal-on-polyethylene THA;
3. To assess the effect of large femoral head THA on range of motion and to study heterotopic ossification as a factor that can compromise range of motion;
4. To study the effects of cobalt and chromium ions on osteoblast cells in-vitro.

OUTLINE OF THE THESIS

Chapter 2 summarizes the literature at the time of conception of our studies. The text also identifies the gaps in knowledge that led to the formation of our four research objectives.

The first objective of this thesis is studied in Chapters 3 and 4. To determine the mid term outcome of 28mm cemented metal-on-metal THA, the 5-year results of a randomised clinical trial (RCT) investigating these two THAs are analysed. The results are described in **Chapter 3. Chapter 4** describes the 10-year results of this same RCT in order to gain insight into the outcome at long term.

In order to answer the second objective, a randomised clinical trial is set up comparing cementless large femoral head metal-on-metal THA with cementless 28mm metal-on-polyethylene THA. The design of this RCT is described in **Chapter 5. Chapter 6** reports on the 1-year clinical outcome, periprosthetic acetabular bone density and serum ion levels of the two groups.

Next, more specific focus will be on range of motion as potential clinical benefit of large head THAs. **Chapter 7** reports on the effect of large head versus 28mm head THAs on range of motion, using the results from the RCT described in chapters 5 and 6. In **Chapter 8** the incidence of heterotopic ossifications (HO) after cementless THA is re-searched, with and without peroperative pulsed lavage, as HO is one of the factors that may compromise range of motion.

Finally, the fourth objective is addressed in **Chapter 9**. It describes the effects of cobalt and chromium ions on human osteoblast-like cells in-vitro.

Chapter 10 provides a general discussion of the studies in this thesis and addresses practical implications and recommendations for future studies. The chapter ends with four general conclusions. **Chapter 11** is a summary of the preceding chapters in both English and Dutch.

REFERENCES

1. AOA. Australian Orthopaedic Association National Joint Replacement Registry, Annual Report. Adelaide: AOA, 2010.
2. Ostendorf M, Johnell O, Malchau H, Dhert WJA, Schrijvers AJP, Verbout AJ. The epidemiology of total hip arthroplasty in The Netherlands and Sweden: present status and future needs. Acta Orthop Scand 2002; 73: 282-286.
3. Smith-Petersen MN. The classic: evolution of mould arthroplasty of the hip joint. J Bone Joint Surg Br 1948; 30: L59.
4. Wiles P. The surgery of the osteoarthritic hip. Br J Surg 1958; 45: 488-97.
5. McKee GK, Watson-Farrar J. Replacement of arthritic hips by the McKee-Farrar prosthesis. J Bone Joint Surg Br 1966; 48: 245-59.
6. Ring PA. Replacement of the hip joint. Ann R Coll Surg Engl 1971; 48: 344-55.
7. Charnley J. Arthroplasty of the hip: a new operation. Lancet 1961; 1: 1129-32.
8. Amstutz HC, Le Duff MJ. Evolution of hip resurfacing. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008: 1-15.
9. Jones LC, Hungerford DS. Cement disease. Clin Orthop Relat Res 1987; 225: 192-206.
10. Purdue PE, Koulouvaris P, Nestor BJ, Sculco TP. The central role of wear debris in periprosthetic osteolysis. HSS J 2006; 2: 102-13.

Verkleedpartijtje, Atlantische Oceaan

Foardwaan leart neidwaan

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2

Background

BACKGROUND

1. To determine the mid and long term clinical outcome of cemented 28mm metal-on-metal THA in comparison with metal-on-polyethylene THA

The resistance to wear shown by some designs of metal-on-metal THAs after two decades in situ encouraged the re-introduction of the metal-on-metal bearing.[1] Adjustments in metallurgy, sphericity and radial clearance were incorporated to create second generation metal-on-metal arthroplasties in the late 1980's.[2, 3] A consensus symposium in 1995 attributed the early failures of first generation metal-on-metal designs to suboptimal surgical technique, excessive or negative clearance, poor fixation and neck/socket impingement.[4] Key factors for long-term success were deemed a polar bearing, sufficient clearance, avoidance of impingement and adequate fixation. Second-generation metal-on-metal wear rates were reported to be 20 to 100 times lower than conventional polyethylene wear rates.[1]

The literature at the time of conception of our studies supported favorable clinical results and acceptable mid-term survival of second generation cementless metal-on-metal THAs. Lombardi et al.[5, 6] reported the 5-year results of 99 patients, comparing 53 cementless metal-on-metal to 46 metal-on-polyethylene THAs. Survival rate was 100% at 5.7 years in both groups, and no radiological or clinical differences were noted between the groups. Others[7] showed equal clinical and radiological performance of 18 cementless metal-on-metal THAs compared to 23 metal-on-polyethylene THAs in a randomized controlled study. After a mean follow-up of 3.2 years, survival was 100% in both groups. Jacobs et al.[8] reported good clinical results and equal radiological outcome in 95 metal-backed metal-on-metal THAs compared to 76 metal-backed metal-on-polyethylene THAs.

Although cementless metal-on-metal THAs showed promising short-term results, much less evidence was available on the outcome of cemented metal-on-metal prostheses. Dorr et al.[9] implanted 70 Metasul metal-on-metal articulations with a cemented Weber cup and cementless or cemented stems. Survival was 98% at an average of 5.2 years in 56 patients. At follow-up, average Harris hip score was 90 points; no acetabular osteolysis was seen, but calcar resorption was noted in two hips. Levai et al.[10] calculated a 94% survival but noted a high number of radiolucencies in 122 Metasul metal-on-metal THAs at an average of almost 4 years follow-up.

In summary, in spite of favourable mid-term clinical outcomes, metal-on-metal THAs had not shown clinical superiority over metal-on-polyethylene yet. Furthermore, long-term randomized controlled trials were absent, especially for cemented metal-on-metal prostheses. For this reason, we formulated the first aim of this thesis: to evaluate the 5-year and 10-year clinical outcome of a cemented 28mm metal-on-metal THA, in comparison to a cemented 28mm metal-on-polyethylene THA, using a randomized trial.

2. To determine the short term clinical outcome and periprosthetic bone implications of cementless large femoral head metal-on-metal THA in comparison with metal-on-polyethylene THA

Proposed benefits of metal-on-metal articulations were a reduction of wear, a subsequent lower incidence of periprosthetic osteolysis and eventually improved prosthetic survival. Clinical studies showed good clinical results and acceptable prosthetic survival[5, 6, 7, 8, 11] but with respect to osteolysis, some studies found unexpected early osteolysis[12], whereas it seemed almost none-existent in other studies.[13, 14] Since osteolysis is implicated in the early phases of prosthetic loosening and failure, it is essential to accurately quantify periprosthetic osteolysis. Conventional radiology is not sensitive and accurate enough to detect small amounts of bone loss, but DEXA is able to detect even small defects in the periprosthetic bone in the acetabulum.[15] For the patient, DEXA results in less radiation exposure than CT.

To our knowledge, no study had quantified periprosthetic acetabular bone changes around metal-on-metal bearings, let alone in a randomized trial. The clinical importance of periposthetic osteolysis and the widespread use of large femoral head metal-on-metal total hip arthroplasty led us to formulate our second objective: to set up a rando-mized clinical trial to evaluate the clinical outcome, periprosthetic acetabular bone density, and serum metal ion levels of cementless large femoral head metal-on-metal THA, in comparison to cementless 28mm metal-on-polyethylene THA.

3. To assess the effect of large femoral head THA on range of motion and to study heterotopic ossification as a factor that can compromise range of motion

Metal-on-metal bearings allowed the use of thinner acetabular components and larger femoral heads, with potential advantages of greater range of motion and less risk of dislocation. Meanwhile, hip simulator and retrieval studies had shown that large femoral heads were also favorable for wear: wear rates decreased with increasing head size >40mm, low radial clearance (120-200 µm) and high carbon content (0.2-0.3%).[16] Large femoral heads increased range of motion (ROM) in hip simulator and biomechanical studies[17] and a large head-neck diameter ratio might be the crucial factor for obtaining large ROM.[18]

Clinical hip ROM after large femoral head hip resurfacing arthroplasty, in comparison to conventional THA, was described in only a few reports.[2, 19] One randomized blinded study compared hip resurfacing to THA, but showed no differences in postoperative ROM.[20]

One of the factors that may compromise range of motion after THA is the formation of heterotopic ossifications (HO). The incidence of HO varies from 8% to 90% depending on risk factors and the criteria used.[21, 22] Especially advanced stages of HO, Brooker grades 3 and 4, are clinically relevant because of pain and hip function impairment.[23, 24, 25] Pulsed lavage around the hip joint and gluteal muscles may prevent HO, is inexpensive and has no known side effects. Only one study on the effect of pulsed lavage has been published and suggested no protective effect on HO formation.[21] In this study, however, all patients received lavage; pulsed or manual with a syringe.

In summary, the clinical benefit of a large femoral head THA in terms of range of motion was still unclear. Hence, we formulated the third objective of this thesis: to evaluate the clinical range of motion after large femoral head THA, in comparison to 28mm THA, using a randomized trial. In addition, we aimed to evaluate the incidence of heterotopic ossifications after cementless THA with and without peroperative pulsed lavage.

4. To study the effects of cobalt and chromium ions on osteoblast cells in-vitro.

As metal-on-metal bearings wear, they generate metal particles, mainly cobalt and chromium. Contrary to the micrometer-sized particles of metal-on-polyethylene bearings, metal-on-metal generated particles are nanometer-sized.[26] These smaller metal particles caused less granulomatous inflammation histologically but were produced in larger numbers[27, 28], hence contributing to an even larger collective metal burden. These nanometer-sized metals have the potential and tendency to corrode if dissolved in solutions such as the synovial fluid, and form metal ions, for instance cobalt^{2+} and chromium^{3+}. Particles larger than 0.1 µm are generally cleared from the joint by macrophages, but nanometer-sized particles and ions are unlikely to stimulate phagocytosis by macrophages.[26] It is well known that metal-on-metal hip arthroplasty gives rise to elevated metal ion levels locally in the synovium, but also distally in the serum and urine.[7, 11, 29] There is no agreement on what level of local or systemic cobalt and chromium ion concentration is normal, let alone acceptable. These ions can be measured in serum and in whole blood and a consensus meeting suggested serum would be preferable.[30] Inductively coupled plasma mass spectroscopy (ICP-MS) and graphite furnace atomic absorption spectrophotometry (GFAAS) are the most commonly used methods. Because of the tendency for outliers in metal ion measurements, the median value is preferred over the mean. An overview paper[11] lists 12 studies on serum or whole blood metal ion levels in different metal-on-metal total hip arthroplasties, ranging from 0.7 to 2.3 µg/L for cobalt and 1.0 to 2.5 µg/L for chromium, with a maximum follow-up of 5 years. Other authors[31] review 8 studies on median serum or whole blood ion levels with various metal-on-metal hip resurfacings; these levels ranged from 0.5 to 4.3 µg/L for cobalt and 0.9 to 5.1 µg/L for chromium, with a maximum 2 year follow-up. Cobalt and chromium levels are influenced by the type, design, and positioning of the implant, with malpositioned (steep) cups showing higher levels; the effects of femoral head size remain controversial[31, 32, 33], although steep cups combined with small femoral heads seem at risk.[34]

Measurement of serum cobalt and chromium concentrations has been advocated as a monitoring tool for high wear rate induced failure of metal-on-metal bearings. In revised metal-on-metal arthroplasty patients, systemic cobalt and chromium ion levels correlated strongly with hip synovial fluid cobalt and chromium ion levels; the latter were approximately 40-50 times higher.[35] In addition, both serum and synovial ion levels correlated strongly to femoral component wear and serum levels above 17-19µg/L were more often associated with intra-operative metallosis.

Biologic effects of cobalt and chromium ions

There are concerns over the long-term biologic effects of metal wear debris and metal ions. These relate to chromosomal damage, possible carcinogenesis, effects on the fetus in women of childbearing age, metal allergy/sensitivity and metal-induced toxicity including bone loss.[11, 31, 33]

Chromosomal aberrations have been described in patients with both metal-on-polyethylene and metal-on-metal arthroplasties.[36] Chromosome translocations and aneuploidy (chromosome gain and loss) were increased in systemic lymphocytes of patients with a metal-on-metal THA.[37] This correlated with molybdenum, but not with cobalt and chromium levels. High levels of chromium in the urine can possibly induce metaplasia of the bladder, as industrial exposure to chromium in metal workers showed an increased bladder cancer risk.[26] In spite of concern for carcinogensis, there is still no confirmed case of implant-induced cancer, and cancer risk appeared not increased after total hip arthroplasty.[38]

Women of childbearing age have been recipients of metal-on-metal arthroplasties. Two reports have shown that metal ions do pass the placenta and the placenta seems to act as a barrier with lower ion concentration in the umbilical cord blood or serum than in the maternal blood resp. serum.[39, 40] Several children have been born to mothers with metal-on-metal bearings, but to date these children have been apparently normal and there are no published incidents. Nonetheless, these studies were all based on mothers with normal functioning implants and relatively 'normal' cobalt and chromium ion concentrations, i.e. <2.5 µg/L. Whether or not elevated maternal and fetal metal ion levels are harmful to the fetus is still unknown. Brodner et al.[29] reviewed the literature on cobalt and chromium teratogenicity in humans and found no evidence for this. Novak et al.[40] reviewed animal (rodent) studies and found fetotoxicity of high doses of hexavalent chromium, but not of trivalent chromium or cobalt.

Metal allergy or sensitivity as a cause for periprosthetic soft-tissue changes is considered as a type-IV delayed-type hypersensitivity reaction driven by T-lymphocytes.[41] Even in low metal wear conditions, a small (1%) number of patients may suffer from this type of allergy or hypersensitivity.[42] Our clinic has reported similar observations in the past.[43] The matching histologic features of the joint tissues have been described as aseptic lymphocytic vasculitis-associated lesions (ALVAL)[41], referring to infiltrates of lymphocytes, often with plasma cells and frequently arranged perivascularly. It is uncertain whether ALVAL is only specific for metal-on-metal implants, but in comparison to polyethylene wear debris, Others[44] showed more lymphocytes and plasma cells and less macrophages in periprosthetic tissues of metal-on-metal bearings. The shift from macrophage-induced to lymphocyte-induced reactions with metal-on-metal implants is supported by others. Reduced leucocyte and myeloid cell numbers were shown in blood of patients with a metal-on-metal THA compared to healthy controls and CD8+ and CD4+ T-cell numbers were negatively affected postoperatively.[45] Another group[46] also found reduced lymfocyte numbers, for CD8+ T-cells especially. B-cell and natural killer numbers did not change. Of note, no reduction of CD8+-cells was seen if combined cobalt and chromium levels were less than 5µg/L. Metal-induced lymphocyte reactivity was found to correlate positively with systemic cobalt and chromium ion levels in metal-on-metal patients in another study.[47] To date, there is no reliable standardized predictive test for metal allergy or hypersensitivity.

Potential toxic effects of larger metal particles on various cell types have been studied extensively in the past, but effects of metal ions are less clear. Toxicity, proliferation and viability of osteoblasts, fibroblasts and lymphocytes have been studied in vitro after exposure with different orthopaedic metals in solution.[48] Cobalt and vanadium were found to be toxic, chromium less so, at concentrations clinically likely to be found in synovial fluid.

Effects of cobalt and chromium ions on bone

Only limited studies have investigated the effects of cobalt and chromium ions on osteoblasts and osteoclasts specifically. The results are mixed. Wang et al.[49] investigated the effects of cobalt, chromium and titanium on human osteoblast-like cells at concentrations up to 100µg/L. They found no influence on cell growth, viability and injury after 72 hours incubation. Fleury et al.[50] studied the effects of rather high levels of cobalt ions (0-10ppm, i.e. 0-10000µg/L) and chromium ions (0-150ppm, i.e. 150000µg/L) on MG-63 osteoblasts in-vitro. Osteoblast cell count decreased in a time and dose-dependent manner, with cobalt more toxic than chromium. Cell viability decreased in the presence of cobalt and chromium ions. Markers of oxidative stress (oxidized and nitrated proteins) revealed time and dose-dependent changes, as did the expression of antioxidant enzymes. On the other hand, others[51] found no significant cytotoxicity of chromium^{3+} ions in osteoblasts (5-20microM). Cobalt ions (10000µg/L) and chromium ions (10000µg/L) added to mature rabbit bone osteoclasts did not induce osteoclast apoptosis, but decreased their size.[52]

A fundamental factor governing bone metabolism by controlling osteoclast formation is the interplay between receptor activator of nuclear factor kappaB (RANK), RANK-ligand (RANKL) and osteoprotegerin (OPG). RANKL, on the surface of the osteoblast, interacts with RANK on the surface of osteoclast precursor cells and stimulates differentiation into mature osteoclasts. RANKL treated mice show increased bone resorption. OPG decreases the number of osteoclasts and mice treated with OPG exhibit lowered osteoclast activity and increased bone volume.[53]

RANK and RANKL play an important role in periprosthetic osteolysis. Both RANK and RANKL were strongly expressed by multinucleated cells containing polyethylene wear debris in hip revision tissues, whereas control tissue stained weakly.[54] A strong correlation was found between RANK, RANKL, volume of bone loss (on CT) and polyethylene wear debris. Polyethylene particles implanted in mice also exhibited high RANKL to OPG ratio's and extensive osteolysis.[55]

In summary, cobalt and chromium ions can have various biological effects. In clinical practice, preventing osteolysis and subsequent loosening after total hip arthroplasty is probably the most important remaining challenge for hip surgeons. Therefore, the effects of metal ions on osteoblasts and osteoclasts are essential. The literature showed that cobalt and chromium ions affect osteoblasts, but only in very high concentrations. Whether or not osteoblasts are affected by cobalt and chromium ions at the concentrations found in patients clinically, is less clear. Furthermore, it is not known whether cobalt and chromium ions influence the osteoblast expression of RANKL and hence the interplay between RANKL, RANK and OPG. Therefore, we formulated the fourth objective of this thesis: to evaluate the effects of cobalt and chromium ions on human osteoblast-like cells in-vitro.

REFERENCES

1. McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, Grigoris P, Amstutz H. In vivo wear of three types of metal on metal hip prostheses during two decades of use. Clin Orthop Rel Res 1996; 329(Suppl):S128-140.
2. Vail TP, Mina CA, Yergler JD, Pietrobron R. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. Clin Orthop Rel Res. 1996; (453):123-131.
3. Beaulé PE, Dorey FJ, LeDuff M, Gruen T, Amstutz HC. Risk factors affecting outcome of metal-on-metal surface arthroplasty of the hip. Clin Orthop Rel Res 2004; (418):87-93.
4. Amstutz HC et al. Metal on metal total hip replacement workshop consensus document. Clin Orthop Relat Res 1996; 329(Suppl):S297-303.
5. Lombardi AV Jr, Mallory TH, Alexiades MM, et al. Short-term results of the M2a taper metal-on-metal articulation. J Arthroplasty. 2001; 16(8 Suppl 1):122-128.
6. Lombardi AV Jr, Mallory TH, Cuckler JM, Williams J, Berend KR, Smith TM. Mid-term results of a polyethylene-free metal-on-metal articulation. J Arthroplasty. 2004; 19(7 Suppl 2):42-47.
7. MacDonald SJ, McCalden RW, Chess DG, et al. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized controlled trial. Clin Orthop Rel Res. 2003; (406):282-296.
8. Jacobs M, Gorab R, Mattingly D, Trick L, Southworth C. Three- to six-year results with the Ultima metal-on-metal hip articulation for primary total hip arthroplasty. J Arthroplasty. 2004; 19(7 Suppl 2):48-53.
9. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. J Bone Joint Surg 2000; 82A:789-798.
10. Levai JP, Descamps S, Roch G, Boisgard S. Early aseptic loosening of cemented cup in metal-on-metal total hip arthroplasties (Article in French). Rev Chir Orthop Reparatrice Appar Mot 2006; 92:575-580.
11. Dumbleton JH, Manley MT. Metal-on-metal total hip replacement: what does the literature say? J Arthroplasty. 2005; 20(2):174-188.
12. Park YS, Moon YW, Lim SJ, Yang JM, Ahn G, Choi YL. Early osteolysis following second-generation metal-on-metal hip replacement. J Bone Joint Surg (Am) 2005, 87-A:1515-1521.
13. Amstutz HC, Grigoris P. Metal on metal bearings in hip arthroplasty. Clin Orthop Rel Res 1996, 329(Suppl):S11-34.
14. Delaunay CP. Metal-on-metal bearings in cementless primary total hip arthroplasty. J Arthroplasty 2004, 19(Suppl 3):35-40.
15. Laursen MB, Nielsen PT, Søballe K: Detection of bony defects around cementless acetabular components in total hip arthroplasty: a DEXA study on 10 human cadavers. Acta Orthop 2006, 77(2):209-217.
16. Medley JB. Tribology of bearing materials. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008:33-38.
17. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR. Biomechanics of large femoral heads: what they do and don't do. Clin Orthop Relat Res 2004, 429:102-107.
18. Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH. Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 2005, 20(1):11-19.
19. Le Duff MJ, Wisk LE, Amstutz HC. Range of motion after stemmed total hip arthroplasty and hip resurfacing: a clinical study. Bull NYU Hosp Joint Dis 2009, 67(2):177-181
20. Lavigne M, Mottard S, Girard J, Vendittoli PA. Range of motion after hip resurfacing and THA: a single-blind randomized clinical study. Proceedings of the 75th Annual American Academy of Orthopaedic Surgeons Meeting; March 5-9, 2008; San Francisco, California, p. 384-385
21. Sneath RJ, Bindi FD, Davies J, Parnell EJ. The effect of pulsed irrigation on the incidence of heterotopic ossification after total hip arthroplasty. J Arthroplasty 2001 Aug;16(5):547-551.

22. Toom A, Haviko T, Rips L. Heterotopic ossification after total hip arthroplasty. Int Orthop 2001;24(6):323-6.
23. Buvanendran A, Kroin JS, Berger RA. Preoperative cyclooxygenase-2 inhibitor treatment reduces the incidence of heterotopic ossification after hip arthroplasty: six-month follow-up. Anesthesiology 2007 Aug;107(2):358-9.
24. Della Valle AG, Ruzo PS, Pavone V, Tolo E, Mintz DN, Salvati EA. Heterotopic ossification after total hip arthroplasty: a critical analysis of the Brooker classification and proposal of a simplified rating system. J Arthroplasty 2002 Oct;17(7):870-5.
25. Kjaersgaard-Andersen P, Ritter MA. Prevention of formation of heterotopic bone after total hip arthroplasty. J Bone Joint Surg Am 1991 Jul;73(6):942-7.
26. Keegan GM, Learmonth ID, Case CP. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Reviews Toxicol 2008, 38:645-674.
27. Doorn PF, Campbell PA, Amstutz HC. Metal versus polyethylene wear particles in total hip replacements. A review. Clin Orthop Relat Res 1996, 329(Suppl): S206-S216.
28. Doorn PF, Mirra JM, Campbell PA, Amstutz HC. Tissue reaction to metal on metal total hip prostheses. Clin Orthop Relat Res 1996, 329(Suppl): S187-S205.
29. Brodner W, Bitzan R, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. J Bone Joint Surg 2003, 85A:2168-2173.
30. MacDonald SJ, Brodner W, Jacobs JJ. A consensus paper on metal ions in metal-on-metal hip arthroplasties. J Arthropl 2004: 19:12-16.
31. Campbell PA, Takamura KM. Reaction to wear products. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008:133-148.
32. Zijlstra WP, Gerritsma-Bleeker CLE, van den Akker-Scheek I, van Raay JJAM. Large head metal-on-metal total hip arthroplasty versus 28mm metal-on-polyethylene hip arthroplasty versus metal-on-metal hip resurfacing: early serum cobalt and chromium ion levels in a randomized and parallel group trial. Poster presented at the 2nd Annual US Comprehensive Course on Total Hip Resurfacing Arthroplasty in Los Angeles, USA, 24-25 Oct 2008.
33. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 2008: 79:734-747.
34. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. J Bone Joint Surg Br. 2008; 90:1291–1297.
35. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, Gill HS: Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg (Am) 2008, 90: 202-208.
36. Case CP. Chromosomal changes after surgery for joint replacement. J Bone Joint Surg 2001;83:1093-1095.
37. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. J Arthropl 2004;19:78-83.
38. Visuri T. Cancer risk after metal on metal hip prosthesis. In: Rieker C, Windler M, Wyss U. Metasul. A metal-on-metal bearing. Bern, Switzerland, Hans Huber, 1998, 149-156.
39. Ziaee H, Daniel J, Datta AK, Blunt S, McMinn DJW. Transplacental transfer of cobalt and chromium in patients with metal-on-metal hip arthroplasty. J Bone and Joint Surg Br. 2007:89: 301-305.
40. Novak CC, Skipor AK, Della Valle CJ, Shott S, Campbell PA, Amstutz HC, Jiranek WA, Pombar XF, Jacobs JJ. Metal Ion Levels in Maternal and Placental Blood Following Metal-on-Metal Arthroplasty. Paper 008, Presented at the 2010 Annual Meeting of the American Academy of Orthopaedic Surgeons. March 9-13. New Orleans, USA
41. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Köster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg 2005; 87A:28-36.
42. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg 2001;83A:428-436.

43. Deutman R, Mulder TJ, Brian R, Nater JP. Metal sensitivity before and after total hip arthroplasty. J Bone Joint Surg 1977; 59A:862-865.
44. Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. J Bone Joint Surg (Am) 2005; 87:18-27.
45. Granchi D, Savarino L, Ciapetti G, Cenni E, Rotini R, Mieti M, Baldini N, Giunti A. Immunological changes in patients with primary osteoarthritis of the hip after total joint replacement. J Bone Joint Surg Br. 2003;85:758-64.
46. Hart A J et al. The association between metal ions from hip resurfacing and reduced T-cell counts. J Bone Joint Surg (Br) 2006; 88: 449-54.
47. Hallab NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ. Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. J Arthroplasty. 2004;19 (Suppl 3):88-93.
48. Hallab NJ, Anderson S, Caicedo M, Brasher A, Mikecz K, Jacobs JJ. Effects of soluble metals on human peri-implant cells. J Biomed Mater Res A. 2005;74:124-40.
49. Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT. Prosthetic metals interfere with the sequencefunctions of the OPG primer sethuman osteblast cells in vitro. Clin Orthop Relat Res 1997 ; 339: 216-226.
50. Fleury C, Petit A, Mwale F, Antoniou J, Zukor DJ, Tabrizian M, Huk OL. Effect of cobalt and chromium ions on human MG-63 osteoblasts in vitro: morphology, cytotoxicity, and oxidative stress. Biomaterials 2006; 27: 3351-3360.
51. Fu J, Liang X, Chen Y, Tang L, Zhang QH, Dong Q. Oxidative stress as a component of chromium-induced cytotoxicity in rat calvarial osteoblasts. Cell Biol Toxicol 2008; 24: 201-212.
52. Rouselle AV, Heymann D, Demais V, Charrier C, Passuti N, Basle MF. Histol Histopathol 2002, 17(4):1025-32.
53. Robling, A, Castillo, A, Turner, C. Biomechanical and molecular regulation of bone remodeling. Annual Review of Biomedical Engineering 2006; 8: 455-498.
54. Holding CA, Findlay DM, Stamenkov R, Neale SD, Lucas H, Dharmapatni AS, Callary SA, Shrestha KR, Atkins GJ, Howie DW, Haynes DR. The correlation of RANK, RANKL TNFalpha expression with bone loss volume and polyethylene wear debris around hip implants. Biomaterials 2006; 27: 5212-5219.
55. Masui T, Sakano S, Hasegawa Y, Warashina H, Ishiguro N. Expression of inflammatory cytokines, RANKL and OPG induced by titanium, cobalt-chromium and polyethylene particles. Biomaterials 2005; 26: 1695-1702.

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3

No superiority of cemented metal-on-metal versus metal-on-polyethylene total hip arthroplasty at 5 years follow-up

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ABSTRACT

A randomized controlled trial was performed to compare the cemented Stanmore metal-on-metal total hip arthroplasty (MM, 102 hips) to the cemented Stanmore metal-on-polyethylene arthroplasty (MP, 98 hips). The primary outcome was clinical performance. Radiological performance, serum cobalt analysis and prosthetic survival were secondary outcome measures. At a mean follow-up of 5.6 years 5 patients were lost to follow-up, 18 died and 4 were revised (3 MM, 1 MP). Harris hip scores improved from 48 to 90 in the metal-on-metal patients ($p<0.001$) and from 46 to 87 in the metal-on-polyethylene patients ($p<0.001$). Oxford hip scores changed from 40 to 19 in the metal-on-metal group ($p<0.001$) and from 40 to 18 in the metal-on-polyethylene group ($p<0.001$). For both Harris and Oxford hip scores, there was no significant difference between the two groups. Periprosthetic radiolucencies were present in 25% of the metal-on-metal hips and in 29% of the metal-on-polyethylene hips ($p=0.711$). Focal osteolysis was absent. Median serum cobalt concentration rose from 0.24 to 0.30 µg/l in the metal-on-polyethylene group ($p=0.104$) and from 0.18 to 0.88 µg/l in the metal-on-metal group ($p<0.001$); this difference was significant ($p=0.001$). We could not find a relation between cobalt concentration and periprosthetic radiolucency. Five year survival with revision for any reason was 97% (95%-CI 93-100%) in the metal-on-metal group and 99% (95%-CI 97-100%) in the metal-on-polyethylene group. All revisions were indicated for aseptic loosening (MM: 3 cup revisions; MP: 1 total revision). At 5-year follow-up, cemented 28mm metal-on-metal total hip arthroplasty shows no clinical superiority over 28mm metal-on-polyethylene arthroplasty.

INTRODUCTION

The results of total hip arthroplasty (THA) are good but polyethylene wear can lead to osteolysis and eventually failure of the implant.[1] Metal-on-metal (MM) articulation is an alternative bearing with a reduced wear rate and it was widely used between 1960 and 1975. The high loosening rate of the McKee-Farrar and other first-generation MM hips and the early success of the Charnley prosthesis were reasons for abandoning the use of MM articulation.[2] Metal-on-metal articulations were reintroduced in the early 1990s to address the emerging problems of polyethylene wear. Adjustments in metallurgy, sphericity and radial clearance have consistently shown improvement in wear performance in second-generation MM articulations.[3, 4] It is hypothesized that this reduction in wear would lead to less osteolysis and superior prosthetic survival. Indeed, published reports show that osteolysis is negligible in association with well-fixed components.[2, 5-7]

In spite of favourable hip simulator study results, metal-on-metal arthroplasty has not shown clinical superiority over metal-on-polyethylene articulation yet.[8] Furthermore, there have only been few reports regarding the outcome of cemented second-generation MM prostheses[9-11] while randomized controlled trials (RCT) are lacking.

The objective of this study was to evaluate and compare cemented total hip prostheses with metal-on-polyethylene interface (MP) with prostheses with metal-on-metal interface (MM). The only difference was the metal inlay in the cup of the MM prosthesis. Primary outcome was clinical performance. Radiological performance, serum cobalt analysis and prosthetic survival were secondary outcome measures. We hypothesized equal clinical performance of the two bearings. The aim of the present report is to evaluate medium-term results.

MATERIALS AND METHODS

Patients

Patients with non-inflammatory degenerative hip joint disease including osteoarthritis, avascular necrosis and traumatic arthritis were included. Exclusion criteria were active infection, revision arthroplasty, marked bone loss precluding adequate fixation, unwillingness or inability to follow instruction, severe vascular insufficiency of the affected limb and severe instability or deformity of the soft tissues precluding stability of the prosthesis.

The randomization procedure was based on sequentially numbered opaque sealed envelopes, produced by an external institution not involved in the selection, care and evaluation of the patients. The study design and procedures were approved by the local Medical Ethical Committee (registration number 97-19). Informed consent was obtained in all patients. The trial was performed in compliance with the Helsinki Declaration.

Operative technique and implants

Five orthopedic surgeons and two orthopedic residents performed the surgery via a posterolateral or direct lateral approach. Antibiotic prophylaxis with a first-generation cephalosporin was given for twenty-four hours intravenously. We used third-generation cementing techniques. Pre-packaged antibiotic-loaded cement was not used. All patients were treated postoperatively following a standardized protocol in terms of analgesia and mobilization. Oral anticoagulation by coumarin-derivate was given 6 weeks postoperatively.

The MP acetabular components were standard Stanmore cups (Biomet, Warsaw, USA) made from ultra-high molecular weight polyethylene (UHMWPE), packaged in an Argon environment and sterilized with gamma irradiation. This polyethylene was not highly cross-linked. The MM (M2A®) cup was manufactured by moulding a block of UHMWPE around a highly polished cobalt-chromium-molybdenum alloy bearing insert, meeting ASTM F1537 requirements. Sizes of the MP and MM acetabular components ranged from 40 to 57 mm. The 28-mm head used in all cases was made of cobalt-chromium-molybdenum alloy and had a radial clearance of 30 to 60 µm. This head was modular. The Stanmore femoral stem had a straight (straight stem) or slightly curved contour (standard stem) and a satin surface finish with a roughness of 0.8 µm Ra; it was made from forged cobalt-chromium-molybdenum alloy and was available in five sizes.

Clinical scores, radiographic evaluation, serum cobalt analysis

Patients were assessed with the Harris Hip Score (HHS)[12, 13] and the Oxford Hip Score.[14] All patients returned for follow-up visits at 6 weeks, at 3, 6 and 12 months and then annually. HHS and Oxford Hip Scores were scored at 1, 2 and 5 years postoperatively. The examiners were not blinded. All complications were noted.

Supine anteroposterior (AP) pelvic hip radiographs (115% magnification) were taken. The radiographs after 6 weeks and after 5 years were evaluated. Radiographs of the stems were reviewed for presence of radiolucent lines and scored according to Gruen et al.[15] Periacetabular radiolucencies were assessed according to De Lee and Charnley.[16] As wear in the cemented MP cup was expected to become apparent only after several years, no protocolized scoring was done for wear. The scoring was undertaken by a radiologist and an independent orthopedic surgeon (M.S.). Date of the X-ray, patient data and type of implant on the X-ray were hidden. None of the patients were cared for by this surgeon.

In a randomly assigned subgroup of patients, venous blood samples were taken preoperatively and 2 and 5 years postoperatively. Serum cobalt concentration was determined by grafite furnace atomic absorption spectrophotometry with Zeeman correction. The threshold for the laboratory was 0.18 μg/l.

Statistical analysis

In order to detect a least clinical relevant difference in Harris Hip Score of 5 points in a non-inferiority design with a standard deviation of 12, 144 hip arthroplasties were needed (alpha 0.05, power 0.80). To compensate for death and loss to follow-up we aimed to include 100 hip arthroplasties in each group. We used the Statistical Package for the Social Sciences (SPSS Inc, Chicago, USA). Non-parametric tests were used for comparisons of means within groups (Wilcoxon's Signed Ranks Test) and between groups (Mann-Whitney Test). Chi-square (Fisher's Exact) tests were employed for analysis of catorical variables. Prosthetic survival was calculated by Kaplan-Meier time series (Mantel-Cox log rank test). A two-sided p-value of <0.05 was assumed to be significant.

RESULTS

Patient groups

Metal-on-metal bearings were allocated to 102 hips; 98 received a metal-on-polyethylene bearing. Five patients underwent staged bilateral hip replacements (1 MM/MM, 1 MP/MP, 3 MM/MP). At baseline, no differences were found between the patients with the MP and MM bearing in terms of gender, operated side, preoperative HHS and Oxford Hip Score (Tables 1-3). Mean age at operation was higher in the MM group.

On average 5 years after surgery, a follow-up was done of all patients. Eighteen patients (19 hips) had died of non-related causes. Five patients were lost to follow-up. Four patients were not able to come to the hospital nor could be interviewed telephonically due to severe medical problems and one had moved and could not be traced. In none of these patients was revision pending or performed and mean HHS at the latest visit was 70. Four patients needed revision surgery. Therefore, a total of 168 patients (172 hips) remained for follow-up at an average of 67 + 6.5 months (range 51-85); 94% had at least 60 months follow-up.

Tabel 1. Preoperative demographics in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups.

	MP	MM	Total	P-value
Number of hips	98	102	200	
Male/female †	20/78	21/81	41/159	1.000
Side (right/left) †	57/41	56/46	113/87	0.671
Mean age (standard deviation) in years ‡	69 (8)	72 (7)	71 (8)	0.018

†P-values were calculated by Chi-Square (Fisher's Exact) tests.
‡P-values were calculated by Mann-Whitney tests.

Tabel 2. Number of hips included and followed-up in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups.

	MP	MM	Number of hips (patients) remaining for analysis
Inclusion			
- Randomized	98	102	200 (195)
- Operated	98	102	200 (195)
Follow-up (mean 66.7 + 6.5 months)			
- Died (not related to - surgical procedure)	11	8	181 (177)
- Lost to follow-up	1	4	176 (172)
- Revised	1	3	172 (168)

Analysis of revisions

All 4 revisions (3 MM, 1 MP) were undertaken because of aseptic cup loosening. The first patient presented with severe coxarthrosis. Within two years postoperatively, radiolucent lines emerged around the MM cup. Twenty-six months postoperatively acetabular revision was performed. The second patient had a 2 x 3 cm cyst in the cranial acetabulum treated by excavation and cement filling. Three months postoperatively a radio-lucent zone in this area suggested insufficient initial fixation of the acetabular component. At revision operation 33 months postoperatively, the cup was loose. The third patient presented with coxarthrosis and protrusion acetabuli. Recurrent posterior dislocations occurred two and three years postoperatively. Fifty-six months postoperatively, X-rays showed a cyst cranial to the cup in the prior protrusion region and subtle cup migration. The patient's loose acetabular component was revised. In all MM cases, the femoral component was well-fixed. One MP patient was revised after 21 months because of pain associated with radiolucent reactions surrounding the stem. At operation all prosthetic material was removed. A cemented THA using bone impaction grafting was implanted. Six years later, a second revision was performed for aseptic stem loosening. A cementless stem was implanted; the cemented cup was well-fixed. At the last visit, the stem showed good osteointegration. In none of these subjects the index operation had been performed by a resident. Infection was ruled out in all cases.

Complications

One femoral shaft perforation occurred. Local complications were 6 hematomas, 5 superficial wound infections (none of these patients needed revision), and 1 posterior dislocation without further sequelae. Cardiovascular and urogenital problems occurred in 12 cases. Two patients suffered a periprosthetic femoral fracture afterward, treated with osteosynthesis without the need for revision.

Clinical outcome

No significant differences were noted between the two groups for either Harris Hip or Oxford scores after 5 years (Table 3). Twenty four patients were reviewed telephonically since they were unable to attend the clinic mostly because of medical conditions unrelated to the hip surgery. Improvement was also seen in the two patients with osteosynthesis for a periprosthetic fracture (HHS 96 and 97).

Table 3. Mean and standard deviation of the Harris Hip (HHS) and Oxford Hip Scores in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups, preoperatively and at follow-up.

	MP		MM		P-value†	
	HHS N=73*	Oxford N=85*	HHS N=75*	Oxford N=87*		
Preop	46 (13)	40 (8)	48 (15)	40 (8)	0.746	0.661
1 yr	85 (13)	18 (7)	86 (8)	19 (8)	0.446	0.461
2 yr	88 (9)	18 (7)	85 (12)	19 (10)	0.025	0.619
5 yr	87 (13)	18 (8)	90 (7)	19 (8)	0.791	0.515
P-value‡	<.001	<.001	<.001	<.001		

*N is the number of hips at 5 year follow-up.
†P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Wilcoxon's Signed Rank tests (preoperatively versus 5 yr).

Radiological outcome

After 5 years both reviewers noted radiolucent lines, especially in Gruen zones 1, 2 and 7 and De Lee & Charnley's zone 3 (Table 4; Figures 1 and 2). Statistical analysis revealed no differences between the groups. None of the radiolucencies indicated implant loosening according to the Zicat criteria.[17]

Table 4. Number of hips showing radiolucent lines on standard anteroposterior pelvic hip radiogrzaphs on average 5 years postoperatively.

	Surgeon			Radiologist		
Zone	MP N=72	MM N=75	P-value*	MP N=72	MM N=75	P-value*
Stem (Gruen)						
1	3	4	1.000	10	14	0.506
2	1	0	0.490	6	11	0.304
3	4	0	0.055	7	3	0.203
4	2	1	0.615	2	3	1.000
5	1	1	1.000	2	2	1.000
6	1	0	0.490	3	3	1.000
7	8	5	0.394	19	17	0.702
Cup (De Lee & Charnley)						
1	2	2	1.000	4	3	0.715
2	4	3	0.715	6	2	0.161
3	9	8	0.800	5	4	0.742
Number of hips with a radiolucency	21 (29%)	19 (25%)	0.711	39 (54%)	41 (55%)	1.000

*Chi-Square (Fisher's Exact) tests were used to test for statistical differences between the metal-on-metal (MM) and metal-on-polyethylene (MP) groups.

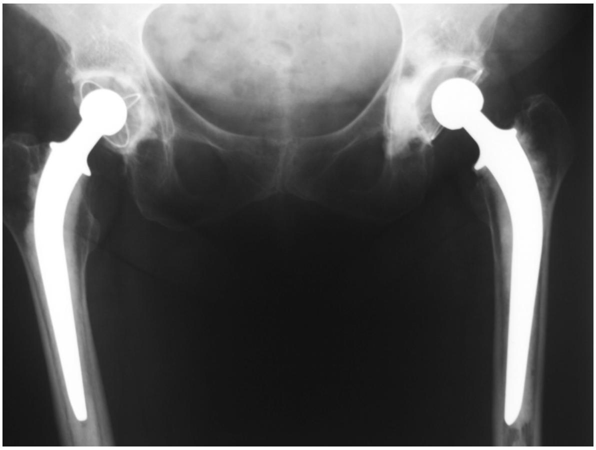

Figure 1. Stanmore metal-on-polyethylene THA at a minimum 8-year follow-up.

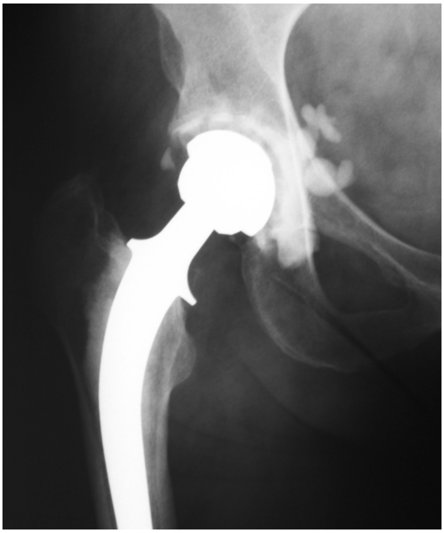

Figure 2. Stanmore metal-on-metal THA at 7-year follow-up.

Serum cobalt analysis

Median cobalt concentration increased 1.3 times in the metal-on-polyethylene group and 4.9 times in the metal-on-metal group (Table 5). At 2 and 5 years cobalt concentration was higher in the MM group. Two MM patients had high cobalt values at 2 years: 7.9 and 15.6 µg/l. The first patient was lost to follow-up regarding her 5 year cobalt concentration but 5 year HHS was 90 and she had no periprosthetic radiolucent lines except for Gruen zone 7. In the latter patient cobalt concentration spontaneously decreased to 0.83 µg/l at 5 years; HHS was 96 and X-rays did not show progressive radiolucencies. One patient showed cobalt levels of 7.0 µg/l at the 5 year follow-up. Her HHS was 88 and she showed no periprosthetic radiolucencies. None of these patients needed revision surgery.

Survivorship

Survival at 5 years (revision for any reason) was 97% in the metal-on-metal group (95%-confidence interval (CI) 93-100%; 85 patients at risk) and 99% for the metal-on-polyethylene articulation (95%-CI 97-100%; 82 patients at risk). There were no significant differences between the two survival curves (p=0.359). The survival rates for aseptic loosening of the acetabular component are similar. Stem survival was 100% in the metal-on-metal group, and 99% (95%-CI 97-100%) in the metal-on-polyethylene group (any reason as well as aseptic loosening). Assuming that all patients lost to follow-up were failures, the worst-case 5 year survival was also calculated:[18] MM survival was 94% (95%-CI 89-99%; 85 patients at risk) and MP survival was 98% (95%-CI 95-100%; 82 patients at risk). This difference was not significant (p=0.121).

Table 5. Median and range of the serum cobalt concentrations (µg/L) in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups, preoperatively and at follow-up.

	MP N=14*		MM N=17*		
	Median	Range	Median	Range	P-value†
Preoperatively	0.24	0.18-0.65	0.18	0.18-1.77	0.185
2 yr	0.18	0.18-1.06	0.77	0.18-15.57	<0.001
5 yr	0.30	0.29-1.65	0.88	0.29-7.02	0.001
P-value‡	0.104		<0.001		

*N is the number of hips at 5 year follow-up; preoperatively and at 2 years N was 24 MM versus 19 MP
†P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Wilcoxon's Signed Rank tests (preoperatively versus 5 yr).

DISCUSSION

In a prospective RCT we found significant clinical improvements with both the metal-on-metal and the metal-on-polyethylene articulations and no difference between the two groups. Periprosthetic radiolucent lines were mainly seen in Gruen zones 1, 2 and 7 and in De Lee & Charnley's zone 3. The number of radiolucencies did not differ statistically between the two articulations. Five year prosthetic survival was 97% (3 revisions) for the metal-on-metal articulation and 99% (1 revision) for the metal-on-polyethylene articulation, with no significant difference.

Studies comparing cemented second-generation metal-on-metal total hip arthroplasty to metal-on-polyethylene were scarce at the time of conception of our study.[19] Given this anecdotal evidence, we aimed to compare these prostheses by means of an RCT. In our clinic, we have been using the Stanmore metal-on-polyethylene prosthesis since 1975.[20, 21] Survival has been shown to be 85% at 22 years.[22] By only changing the metal inlay in the cemented cup we could ensure that the only varying parameter was the articulation and we could eliminate learning curves or prosthetic design failures. Certain limitations have to be considered. It was difficult to perform complete follow-up of older people with severe health problems who were well willing yet unable to visit the clinic, but most could be reviewed via the Oxford questionnaires. The mean age of the MM patients was 3 years higher than in the MP group, suggesting inadequate randomization and selection bias. Since the age difference was small and preoperative Harris and Oxford Hip Scores were equal, we feel the groups were comparable. Although the same criterion was used (presence of a radiolucent line from <1mm), the well established Gruen and De Lee & Charnley zones were used and the assessors were experienced, the radiologist noted more radiolucencies than the orthopedic surgeon. The surgeon probably directly interpreted the radiolucencies based on his clinical and prosthetic revision surgery experience. In our view, this does not change the results since the radiologist also noted no difference between the two groups (Table 4).

With respect to clinical improvement and survival, our results are comparable to the work of Dorr et al.,[9] implanting 70 Metasul metal-on-metal articulations with a cemented Weber cup. Survival was 98% at 5.2 years. Calcar resorption was noted in two hips. Levai et al. calculated a 94% survival in 122 cemented Metasul metal-on-metal hips at 3.7 years; eleven hips were radiographically loose.[10] A similar (27%) radiolucency rate as in our study was found by Nich et al.[11]

As to why metal-on-metal bearings fail, several factors need to be considered: acetabular fixation, femoral head size, carbon-content and serum metal ion concentration. Satisfying results of cementless fixation have been shown by several RCTs comparing metal-on-metal to metal-on-polyethylene THAs.[23-26] In general, clinical and radiological performance was equal, osteolysis was hardly seen, but none of the studies proved superiority of the metal-on-metal bearing over polyethylene, follow-up was relatively short (3.2 to 5.7 years) and the patients were relatively young. With respect to femoral head size and carbon content, hip simulator and retrieval studies have shown that metal-on-metal wear rates decrease with increasing head size (>40mm), low radial clearance (120-200 μm) and high carbon content.[27] The radial clearance was satisfactorily low (30-60 μm), carbon content high (0.2-0.3%), but the 28mm articulation may not have developed the optimal fluid film lubrication needed for low wear performance.

Measurement of serum cobalt and chromium concentrations has been advocated as a monitoring tool for high wear rate induced failure of metal-on-metal bearings. We measured a median serum cobalt concentration of 0.88 μg/l in the metal-on-metal bearings and 0.30 μg/l in the metal-on-polyethylene prostheses. Brodner et al. found a 0.7 μg/l concentration after 5 years[28] and 0.75 μg/l after 10 years.[29] We could not find a relation between cobalt concentration and periprosthetic radiolucency. Patients with high ion levels all showed high Harris Hip scores, few or no periprosthetic radiolucencies, and none were revised.

Concerns over the long-term biologic effects of metal-metal wear particles remain.[8, 30, 31] Chromosomal and DNA damage are mentioned, as well as kidney disease, metal-induced toxicity and metal allergy or sensitivity. Metal sensitivity seems a type IV delayed-type hypersensitivity and we have reported this phenomenon in the past.[32] The histologic features are referred to as aseptic lymphocytic vasculitis-associated lesions (ALVAL).[33] In all, the enthusiasm for metal-on-metal bearings prompted by the milder periprosthetic tissue reaction and absence of osteolysis should perhaps be reconsidered, especially in the absence of long-term randomized controlled trials. However, in none of our revised patients was ALVAL described by our pathologists and we could not relate the cause of revision to metal allergy or sensitivity. Our results do not indicate clinically harmful effects of the metal-on-metal articulation so far.

This randomized controlled trial compared cemented second-generation metal-on-metal total hip arthroplasty to metal-on-polyethylene hip arthro plasty to metal-on-polyethylene hip arthroplasty at 5 years follow-up. We found equal clinical improvement with both prostheses. Cobalt serum levels were higher in the metal-on-metal patients. We did not observe less periprosthetic radiolucencies with the metal-on-metal bearing, nor did we see improved prosthetic survivorship. Given the absence of clinical superiority of the cemented metal-on-metal bearing so far, we continue using the metal-on-polyethylene prosthesis in our clinic. We will report on the 10 year results in the future.

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Disclosure

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REFERENCES

1. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg Am. 1992; 74:849-863.
2. Amstutz HC, Grigoris P. Metal on metal bearings in hip arthroplasty. Clin Orthop Rel Res. 1996; (329 Suppl):S11-34.
3. Vail TP, Mina CA, Yergler JD, Pietrobron R. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. Clin Orthop Rel Res. 1996; (453):123-131.
4. Beaulé PE, Dorey FJ, LeDuff M, Gruen T, Amstutz HC. Risk factors affecting outcome of metal-on-metal surface arthroplasty of the hip. Clin Orthop Rel Res. 2004; (418):87-93.
5. Delaunay CP. Metal-on-metal bearings in cementless primary total hip arthroplasty. J Arthroplasty. 2004; 19(8 Suppl 3):35-40.
6. Schmidt M, Weber H, Schön R. Cobalt chromium molybdenum metal combination for modular hip protheses. Clin Orthop Relat Res. 1996; (329 Suppl):S35-47.
7. McKellop H, Park SH, Chiesa R, et al. In vivo wear of three types of metal on metal hip prostheses during two decades of use. Clin Orthop Rel Res. 1996; (329 Suppl):S128-140.
8. Dumbleton JH, Manley MT. Metal-on-metal total hip replacement: what does the literature say? J Arthroplasty. 2005; 20(2):174-188.
9. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. J Bone Joint Surg Am. 2000; 82(6):789-798.
10. Levai JP, Descamps S, Roch G, Boisgard S. Early aseptic loosening of cemented cup in metal-on-metal total hip arthroplasties [Article in French]. Rev Chir Orthop Reparatrice Appar Mot. 2006; 92(6):575-580.
11. Nich C, Rampal V, Vandenbussche E, Augereau B. Metal-metal-backed polyethylene cemented hip arthroplasty: mid-term results [Article in French]. Rev Chir Orthop Reparatrice Appar Mot. 2006; 92(2):118-124.
12. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fratures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am. 1969; 51(4):737-755.
13. Söderman P, Malchau H. Is the Harris Hip Score system useful to study the outcome of total hip replacement? Clin Orthop Rel Res. 2001; (384):189-197.
14. Gosens T, Hoefnagels NH, de Vet RC, et al. The “Oxford Heup Score”: the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. Acta Orthop. 2005; 76(2):204-211.
15. Gruen TA, McNeice GM, Amstutz HC. “Modes of failure” of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res. 1979; (141):17-27.
16. DeLee JG, Charnley J. Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop. 1976; (121):20-32.
17. Zicat B, Engh CA, Gokcen E. Patterns of osteolysis around total hip components inserted with and without cement. J Bone Joint Surg Am. 1995; 77(3):432-439.
18. Murray DW, Carr AJ, Bulstrode C. Survival analysis of joint replacements. J Bone Joint Surg Br. 1993; 75(5):697-704.
19. Dobbs HS. Survivorship of total hip replacements. J Bone Joint Surg Br. 1980; 62(2):168-173.
20. Van der Schaaf DB, Deutman R, Mulder TJ. Stanmore total hip replacement: a nine- to ten-year follow-up. J Bone Joint Surg Br. 1988; 70(1):45-48.
21. Alsema R, Deutman R, Mulder TJ. Stanmore total hip replacement. A 15- to 16-year clinical and radiographic follow-up. J Bone Joint Surg Br. 1994; 76(2):240-244.
22. Gerritsma-Bleeker CL, Deutman R, Mulder TJ, Steinberg JD. The Stanmore total hip replacement. A 22-year follow-up. J Bone Joint Surg Br. 2000; 82(1):97-102.
23. Lombardi AV Jr, Mallory TH, Alexiades MM, et al. Short-term results of the M2a taper metal-on-metal articulation. J Arthroplasty. 2001; 16(8 Suppl 1):122-128.
24. Lombardi AV Jr, Mallory TH, Cuckler JM, Williams J, Berend KR, Smith TM. Mid-term results of a polyethylene-free metal-on-metal articulation. J Arthroplasty. 2004; 19(7 Suppl 2):42-47.
25. MacDonald SJ, McCalden RW, Chess DG, et al. Metal-on-metal versus polyethylene in hip

arthroplasty: a randomized controlled trial. Clin Orthop Rel Res. 2003; (406):282-296.
26. Jacobs M, Gorab R, Mattingly D, Trick L, Southworth C. Three- to six-year results with the Ultima metal-on-metal hip articulation for primary total hip arthroplasty. J Arthroplasty. 2004; 19(7 Suppl 2):48-53.
27. Medley JB. Tribology of bearing materials. In: Amstutz HC (ed.) Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier; 2008: 33-38.
28. Brodner W, Bitzan R, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. J Bone Joint Surg Am. 2003; 85(11):2168-2173.
29. Grübl A, Marker M, Brodner W, et al. Long-term follow-up of metal-on-metal total hip replacement. J Orthop Res. 2007; 25(7):841-848.
30. Campbell PA and Takamura KM. Reaction to wear products. In: Amstutz HC (ed.) Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier; 2008: 133-148.
31. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop. 2008; 79(6):734-47.
32. Deutman R, Mulder TJ, Brian R, Nater JP. Metal sensitivity before and after total hip arthroplasty. J Bone Joint Surg Am. 1977; 59(7):862-865.
33. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am. 2005; 87(1):28-36.

4

San Cristobal, Galapagos

It komt er net op oan hoe âld men is, mar hoe’t men ald is.

Het komt er niet op aan hoe oud men is, maar hoe men oud is.

No superiority of cemented metal-on-metal over metal-on-polyethylene total hip arthroplasty in a randomized trial at 10-year follow-up

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ABSTRACT

In a randomized controlled trial, 102 cemented Stanmore 28-mm metal-on-metal total hip arthroplasties (THAs) were compared to 98 metal-on-polyethylene THAs in 195 patients. At a mean follow-up of 10 years, 11 patients (11 hips) were lost to follow-up, 53 patients (55 hips) died, and 6 patients (6 hips) underwent revision. Average age of the surviving patients was 79 years. Harris Hip Scores and Oxford Hip Scores had increased significantly in both groups ($p<.001$). Ten years postoperatively, mean Harris Hip Score was 86 in the metal-on-metal patients and 87 in the metal-on-polyethylene patients ($p=.441$); Oxford Hip Scores were 27 and 24, respectively ($p=.494$). Wear was present in 30 of 52 polyethylene cups. Periprosthetic radiolucencies were seen in 57% of the metal-on-metal patients and in 52% of the metal-on-polyethylene patients ($p=.680$); they were mainly seen in DeLee & Charnley's zones 1 and 2. Serum cobalt and chromium concentration were higher in the metal-on-metal group (cobalt 1.1, chromium 1.0 vs 0.5 and 0.5 µg/L, respectively; $p<.001$). Patients with high ion levels (maximum 9.5 and 11 µg/L, respectively) all showed high Harris Hip Scores and few or no periprosthetic radiolucencies, and none were revised. Ten-year survival was 95.5% in the metal-on-metal group (4 revisions) and 96.8% in the metal-on-polyethylene group (2 revisions; $p=.402$). All revisions were indicated for aseptic loosening. One case of aseptic lymphocytic vasculitis-associated lesions (ALVAL) and no pseudotumors were observed. The absence of clinical superiority of the cemented metal-on-metal bearing and the concerns over their biological effects have led us to favor the cemented metal-on-polyethylene THA.

INTRODUCTION

The long-term results of total hip arthroplasty (THA) are hampered by polyethylene wear which can lead to osteolysis and eventually failure of the implant.[1] Metal-on-metal (MM) articulation is an alternative bearing with a reduced wear rate. It was widely used between 1960 and 1975. MM articulation was discouraged by the early success of the Charnley prosthesis and the high loosening rate of the McKee-Farrar and other first-generation MM hips.[2] The emerging adverse reactions of polyethylene wear lead a resurgence of metal-on-metal articulations in the early 1990s. Improved wear-performance was achieved by modifications in metallurgy, sphericity and radial clearance in second-generation MM articulations.[3,4] It is hypothesized that the reduction in prosthetic wear would lead to less osteolysis and superior prosthetic survival. Indeed, studies have reported negligible osteolysis in well-fixed components.[2,5-7]

However, metal-on-metal arthroplasty has not demonstrated clinical superiority over metal-on-polyethylene articulation yet,[8] regardless of favourable hip simulator study results. Moreover, reports regarding the outcome of cemented second-generation MM prostheses are scarce[9-11] and randomized controlled trials (RCT) and long-term follow-up studies are lacking.

Our objective was to evaluate and compare cemented total hip prostheses with a metal-on-polyethylene articulation (MP) with prostheses with a metal-on-metal articulation (MM). The metal inlay in the cup of the MM articulation was the only difference between both prostheses. Clinical performance was the primary outcome. Radiological performance, serum metal ion analysis and prosthetic survival were secondary outcome measures. We hypothesized equal clinical performance of the two bearings. The aim of the present report is to describe the 10-year follow-up results. The 5-year results were published earlier.[12]

MATERIALS AND METHODS

Patients

Consecutive patients with non-inflammatory degenerative hip joint disease including osteoarthritis, avascular necrosis and traumatic arthritis were included. Exclusion criteria were active infection, revision arthroplasty, marked bone loss precluding adequate fixation, unwillingness or inability to follow instruction, severe vascular insufficiency of the affected limb and severe instability or deformity of the soft tissues precluding stability of the prosthesis.

The randomization procedure was based on sequentially numbered opaque sealed envelopes, produced by an external institution not involved in the selection, care and evaluation of the patients. The local Medical Ethical Committee approved the study design and procedures (registration number 97-19). Informed consent was obtained in all patients. The trial was conducted in compliance with the Helsinki Declaration.

Operative technique and implants

The surgeries were performed in 1998 and 1999 by five orthopaedic surgeons and two orthopaedic residents. Both the posterolateral and direct lateral approach were used. Antibiotic prophylaxis with a first-generation cephalosporin was given for twenty-four hours intravenously. We used third-generation cementing techniques. Postoperative analgesia and mobilization adhered to a standardized protocol in all patients. An oral coumarin-derivate was given for 6 weeks postoperatively.

The MM Stanmore cup (M2A®, Biomet, Warsaw, United States of America) was manufactured by moulding a block of ultra-high molecular weight polyethylene (UHMWPE) around a highly polished cobalt-chromium-molybdenum alloy bearing insert, meeting ASTM F1537 requirements. The MP acetabular components were standard Stanmore cups made from UHMWPE, packaged in an Argon environment and sterilized with gamma irradiation. This polyethylene was not highly cross-linked. Both types of acetabular components were available in sizes from 40 to 57 mm. The 28-mm head used in all cases had a radial clearance of 30 to 60 μm and was made of cobalt-chromium-molybdenum alloy. This head had various neck lengths if necessary. The Stanmore femoral stem had a straight (straight stem) or slightly curved contour (standard stem) and a satin surface finish with a roughness of 0.8 μm Ra. The stem was made from forged cobalt-chromium-molybdenum alloy; five sizes were available.

Clinical scores, radiographic evaluation, metal ion analysis

Patients were assessed pre-operatively with the Harris Hip Score (HHS)[13,14] and the Oxford Hip Score.[15] All patients returned for follow-up at regular intervals, at least annually. HHS and Oxford Hip Scores were scored at 1, 5 and 10 years postoperatively. The examiners were not blinded.

At each follow-up visit supine anteroposterior (AP) pelvic hip radiographs (115% magnification) were taken. See Figure 1 for an example. At the 10 year follow-up, radiographs of the stems were reviewed for presence of radiolucent lines and scored according to Gruen et al.[16] and periacetabular radiolucencies were assessed according to De Lee and Charnley.[17] Radiological loosening and migration were noted if present. Scoring was undertaken by a senior orthopaedic registrar (WPZ) and a senior orthopaedic surgeon (JJAMVR) and consensus was sought.

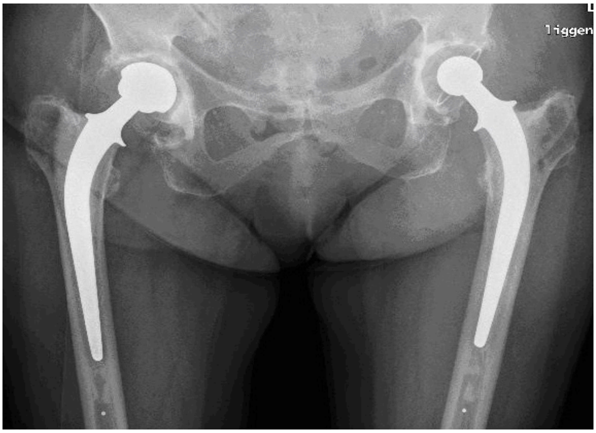

Figure 1: Stanmore metal-on-metal (right) and metal-on-polyethylene (left) THAs at 10- and 9-year follow-up, respectively.

In a subgroup of patients, venous blood samples were taken. Cobalt ion concentrations were determined preoperatively and 5 and 10 years postoperatively; chromium ion concentrations were only measured 10 years postoperatively. We used inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7500 Series, Agilent Technologies, United States of America) and grafite furnace atomic absorption spectrophotometry with Zeeman correction (GFAAS; Varian 220Z, Varian Inc., United States of America). The reference values of our laboratory were <6.8 nmol/l (0.40 µg/l) for cobalt and <48 nmol/l (2.50 µg/l) for chromium.

Statistical analysis

In order to detect a least clinical relevant difference in Harris Hip Score of 5 points in a non-inferiority design with a standard deviation of 12, 144 hip arthroplasties were needed (alpha 0.05, power 0.80). To compensate for death and loss to follow-up, 100 hip arthroplasties in each group were aimed for.

We used the Statistical Package for the Social Sciences (SPSS Inc, Chicago, USA). Non-parametric tests were used for comparisons of means within groups (Wilcoxon's Signed Ranks test) and between groups (Mann-Whitney test). Chi-square (Fisher's Exact) tests were employed for analysis of categorical variables. Prosthetic survival was calculated by Kaplan-Meier time series (Mantel-Cox log rank test). A two-sided p-value of <0.05 was adopted as significance criterion.

RESULTS

Patient groups

Ninety-eight metal-on-polyethylene articulations and 102 metal-on-metal articulations were allocated to 195 patients. Five patients underwent staged bilateral hip replacements (1 MM/MM, 1 MP/MP, 3 MM/MP). No differences were present between the patients groups in terms of gender, operated side, preoperative HHS and Oxford Hip Score (Tables 1 and 3). Mean age at operation was higher in the MM group.

In 2008 and 2009, on average 10 years after surgery, all patients were contacted to come in for review. Fifty-three patients (55 hips) had died of non-related causes. The number of deaths did not differ between the 2 prosthetic groups (Chi-Square Fisher's Exact test, p=0.528). Eleven patients (11 hips) had moved or were lost to follow-up. Eight patients (8 hips) did not want to cooperate anymore. Eighteen patients (18 hips) were not able to come to the hospital due to severe medical problems. In none of these patients was revision performed or pending. Six patients (6 hips) needed revision surgery. Consequently, a total of 102 hips (55 MP, 47 MM; 99 patients) remained for follow-up at an average of 121 + 4 months (range 109-128); see Table 2.

Clinical outcome

Both groups improved significantly (Table 3). Harris hip and Oxford hip scores at 10-year follow-up did not differ between the two groups. Eleven out of the eighteen patients with severe medical morbidity were reviewed by Oxford scores alone since they were unable to attend the clinic.

Table 1. Preoperative demographics in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups.

	MP	MM	Total	P-value
Number of hips	98	102	200	
Male/female †	20/78	21/81	41/159	1.000
Side (right/left) †	57/41	56/46	113/87	0.671
Mean age (standard deviation) in years ‡	69 (8)	72 (7)	71 (8)	0.018

†P-values were calculated by Chi-Square (Fisher's Exact) tests.
‡P-values were calculated by Mann-Whitney tests.

Table 2. Number of hips included and followed-up in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups.

	MP	MM
Randomized and operated	98	102
Died (not related to surgical procedure)	25	30
Lost to follow-up	4	7
Refused cooperation	4	4
Unable due to comorbidity	8	10
Revised	2	4
Remaining for follow-up (mean 121 +/- 4 months)	55	47

Table 3. Mean and standard deviation of the Harris Hip (HHS) and Oxford Hip Scores in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups, pre-operatively and at follow-up.

	MP		MM		P-value †	
	HHS	Oxford	HHS	Oxford	HHS	Oxford
Preoperatively	46 (13)	40 (8)	48 (15)	40 (8)	0.746	0.661
1 yr	85 (13)	18 (7)	86 (8)	19 (8)	0.446	0.461
5 yr	87 (13)	18 (8)	90 (7)	19 (8)	0.791	0.515
10 yr	87 (10)	24 (9)	86 (10)	27 (13)	0.441	0.494
P-value‡	<0.001	<0.001	<0.001	<0.001		

†P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Wilcoxon's Signed Rank tests (preoperatively versus 10 yr).

Complications

One femoral shaft perforation occurred intra-operatively without long-term clinical sequelae (MP group). There were 6 hematomas, 5 superficial wound infections (none of these patients needed revision), and 1 posterior dislocation without further sequelae. Cardiovascular and urogenital events occurred in 12 patients. Two patients (1 MP, 1 MM) suffered a periprosthetic femoral fracture 5 years postoperatively. These were treated with osteosynthesis; revision was not needed. Long-term clinical improvement was seen in both patients.

Radiological outcome

After 10 years no focal osteolysis was seen, but radiolucent lines were noted especially in De Lee & Charnley's zone 1 and 2 and to a lesser extent in Gruen zones 1 and 7 (Table

4). Statistical analysis revealed no differences between the groups. Two cups (1 MM, 1 MP) were radiologically loose according to the Zicat criteria,[18] but these patients had no complaints (HHS 81 and 83). All other cups were stable. Polyethylene wear was noted in 30 of the 52 polyethylene cups.

Serum cobalt and chromium analysis

Postoperative cobalt and chromium concentrations were significantly higher in the MM group. Median cobalt concentration increased 2.1 times in the metal-on-polyethylene group and 6.1 times in the metal-on-metal group (Table 5). One patient showed cobalt levels of 7.0 µg/l at the 5-year follow-up. Her HHS was 88, her Oxford-score 12 and she showed no periprosthetic radiolucencies at 5 years. At the 10 year review she was not able to come to the hospital due to comorbidity (mamma carcinoma) but her Oxford-score was 14. One patient presented with a cobalt level of 11 µg/l and a chromium level of 9.5 µg/l at the 10 year follow-up. She had no complaints, her HHS was 95, her Oxford-score 14 and no radiolucencies were seen. All other 10 year cobalt and chromium levels were below 2.5 µg/l. None of these patients needed revision surgery.

Table 4. Number of hips showing radiolucent lines on standard anteroposterior pelvic hip radiographs on average 10 years postoperatively.

Zone	MP	MM	P-value*
	N=52	N=42	
Stem (Gruen)			
1	5	6	0.532
2	0	1	0.447
3	0	1	0.447
4	1	0	1.000
5	0	0	-
6	0	0	-
7	4	0	0.125
Cup (De Lee & Charnley)			
1	17	13	1.000
2	16	9	0.495
3	9	8	1.000
Number of hips with a radiolucency	27 (52%)	24 (57%)	0.680

*Chi-Square (Fisher's Exact) tests were used to test for statistical differences between the metal-on-metal (MM) and metal-on-polyethylene (MP) groups.

Table 5. Median and range of the serum cobalt and chromium concentrations (µg/L) in the metal-on-polyethylene (MP) and metal-on-metal (MM) groups, preoperatively and at follow-up.

	MP		MM		P-value†
	N=13*		N=17*		
	Median	Range	Median	Range	
Preoperatively (cobalt)	0.24	0.18-0.65	0.18	0.18-1.77	0.185
5 yr (cobalt)	0.30	0.29-1.65	0.88	0.29-7.02	0.001
10 yr (cobalt)	0.50	0.40-1.30	1.10	0.50-11.0	<0.001
10 yr (chromium)	0.50	0.50-0.90	1.00	0.50-9.5	<0.001
P-value‡	0.037		0.042		

*N is the number of hips at 10 year follow-up; preoperatively N was 24 MM versus 19 MP
†P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Wilcoxon's Signed Rank tests (cobalt preoperatively versus 10 yr).

Analysis of revisions

All 6 revisions (4 MM, 2 MP) were undertaken because of aseptic loosening. In the MP group one patient was revised after 21 months because of pain associated with radiolucent reactions surrounding the stem. All prosthetic material was removed. A cemented THA using bone impaction grafting was implanted. In a second MP patient radiographic loosening was noted of both the stem and cup after nine years. A total revision was performed ten years postoperatively.

The first MM acetabular revision surgery was performed at 26 months postoperatively for pain and emerging radiolucent lines around the cup. The second patient had a 2 x 3 cm cyst in the cranial acetabulum that was initially treated by excavation and cement filling. Three months postoperatively a radiolucent zone in this area emerged, suggesting insufficient initial fixation of the MM cup. At revision operation 33 months postoperatively, the cup was loose. The third patient suffered from protrusio acetabuli and arthrosis. Two and three years postoperatively recurrent posterior dislocations occurred. Fifty-six months postoperatively, X-rays showed a cyst cranial to the MM acetabular component in the prior protrusion region and subtle migration. The loose cup was revised. The femoral component was well-fixed in all the above patients. The fourth patient had a history of tuberculosis in both her lung and hip but had been asymptomatic for at least 15 years. Intra-operative cultures and histology ruled out infection and tuberculosis at the time of implantation of the MM hip. Seven years postoperatively progressive radiolucencies were noted and a Girdlestone hip was created due to insufficient bonestock for reimplantation. Histology showed no signs of tuberculosis.

In all of the revision cases infection was ruled out by culture and/or histology. Lymphocytic infiltration was seen in only one case (the second MM revision described above). In this patient's periprosthetic tissues, eosinophiles and macrophages were also seen. Macrophage presence was noted in two other patients as well (1 MP, 1 MM). Giant cell proliferation was described in one case (the first MM patient above).

Survivorship

Survival at 10 years (revision for any reason as well as aseptic loosening was 95.5% in the metal-on-metal group (95%-confidence interval (CI) 91.2-99.8%; 37 patients at risk) and 96.8% for the metal-on-polyethylene articulation (95%-CI 92.3-100%; 46 patients at risk). There were no significant differences between the two survival curves (Mantel-Cox log rank test, p=0.402). The survival rates for the acetabular component were similar. Stem survival was 98.6% (95%-CI 96.1-100%) in the metal-on-metal group, and 96.8% (95%-CI 92.3-100%) in the metal-on-polyethylene group (any reason as well as aseptic loosening; Mantel-Cox log rank test, p=0.606). Assuming that all patients lost to follow-up (including those that had moved, were unable to attend the clinic or did not want to cooperate anymore) were also failures, the worst-case 10-year survival was also calculated:[19] MM survival was 80.5% (95%-CI 70.9-90.1%) and MP survival was 86.2% (95%-CI 77.6-94.8%). This difference was not statistically significant.

DISCUSSION

The objective of the present randomized controlled trial was to evaluate and compare cemented metal-on-metal total hip articulations with metal-on-polyethylene articulations. Both articulations lead to significant clinical improvements. At 10-year follow-up, Harris and Oxford hip scores did not differ between the two groups. Focal osteolysis was not observed. Periprosthetic radiolucent lines were mainly seen in De Lee & Charnley's zone 1 and 2 and the frequency of radiolucencies did not differ statistically between the two articulations. Ten-year prosthetic survival was 95.5% (4 revisions) for the metal-on-metal articulation and 96.8% for the metal-on-polyethylene articulation (2 revisions), with no statistically significant difference.

We aimed to compare metal-on-metal and metal-on-polyethylene articulations as comparative studies on cemented second-generation metal-on-metal total hip arthroplasty were scarce at the time of conception of our study.[20] In our clinic, we have been using the Stanmore metal-on-polyethylene prosthesis since 1975.[21, 22] We have shown survival to be 85% at 22 years.[23] By only changing the metal inlay in the cemented cup we could ensure that the only varying parameter was the articulation and we could eliminate learning curves or prosthetic design failures.

Our study suffers from limitations. Our patients were relatively old at the time of entry into the trial. Many patients therefore died before the 10-year review. The surviving patients were 79 years old on average, and quite a few patients were unable to visit the clinic due to co-morbidity. Some could be reviewed via the Oxford questionnaires. One can argue that our total of 102 hips remaining for follow-up is less than the calculated sample size of 144 that was needed tot detect a 5 point difference in Harris Hip Score. HHS standard deviation at 10 years was 10 however instead of the assumed 12. This means that 51 hips in each group were sufficient to detect a 5 point difference.

With respect to clinical improvement and survival our results are comparable to other reports. Dorr et al. analyzed 70 Metasul metal-on-metal articulations with a cemented Weber cup. [9] Survival was 98% at 5.2 years in 56 patients; average HHS was 90 points. Acetabular osteolysis was not seen, but calcar resorption was noted in two hips. A 94% survival at 3.7 years follow-up was shown by Levai et al., describing 122 cemented Metasul metal-on-metal hips.[10] They noted radiographically probable loosening in 11 hips and when the patients with progressing radiolucencies were taken into account the calculated 5-year survival decreased to 80%. This group therefore discontinued cementing the Metasul cup. Eswaramoorthy et al. describe 6 revisions in 85 Metasul metal-on-metal hips at 10.8 years follow-up.[11] A cemented cup was implanted in half of the subjects. Survivorship was 94% at ten years. Lazennec recently described their 9-year results for the cemented Metasul cup.[24] Survival rates were between 89% (revision for any reason) and 91% (revision for aseptic cup loosening). This group stopped using the cemented metal-on-metal cup.

Cementless metal-on-metal total hip arthroplasties have been tested in RCTs and have shown satisfying short and medium-term results. Lombardi et al. reported the 5-year results of 53 metal-on-metal versus 46 metal-on-polyethylene THAs.[25, 26] Survival rate was 100% at 5.7 years in both groups; radiological and clinical differences were absent. MacDonald et al. showed equal clinical and radiological performance of 18 cementless metal-on-metal THAs compared to 23 metal-on-polyethylene THAs.[27] After a mean follow-up of 3.2 years, survival was 100% in both groups. Jacobs et al. reported good clinical results and equal radiological outcome in 95 Ultima metal-on-metal cups compared to 76 polyethylene cups.[28] In all, none of the studies proved superiority of the metal-on-metal bearing over polyethylene.

From a tribological point of view, the main advantages of metal-on-metal over conventional metal-on-polyethylene are the low wear-rate and the use of larger, more stable heads. Several factors appear crucial for this low wear performance. Hip simulator and retrieval studies have shown that metal-on-metal wear rates decrease with increasing head size (>40mm), low radial clearance (120-200 μm) and high carbon content.[29] The radial clearance in our study was satisfactorily low (30-60 μm), carbon content was high (0.2-0.3%), but the 28mm articulation may not have developed the optimal fluid film lubrication necessary for low wear-rates. We were unable to measure wear in our metal-on-metal articulations as this is impossible through conventional radiographs. We did see wear in a large proportion (30/52) of the metal-on-polyethylene articulations. The polyethylene used was not highly-crosslinked. Had this been the case, the observed polyethylene wear might have been less. The frequent presence of polyethylene wear indicates its fragility in long-term usage.

The value of periprosthetic radiolucencies in metal-on-metal articulations remains open to debate. A high number of these lucencies were present in both the metal-on-polyethylene (52%) and the metal-on-metal articulations (57%). Focal osteolysis was not seen. Lazennec found radiolucent lines and osteolysis in 26% of the cemented Metasul cups after 9 years.[24] The higher age and thus inferior bone quality of our patients may partly explain these lucencies, as may cementing technique and initial fixation. Higher friction torques generated by the metal-on-metal articulation may stress the bone cement interface more than in metal-on-polyethylene articulation. Whether these lucencies are suggestive of future cup failures remains to be seen in the next 5 years.

High serum metal ion concentrations may indicate failure of a metal-on-metal implant. Hence we monitored systemic cobalt and chromium levels. Median serum cobalt concentration at 10-year follow-up was 1.10 µg/l in the metal-on-metal bearings and 0.50 µg/l in the metal-on-polyethylene bearings; medium chromium concentration was 1.00 and 0.50 µg/l, respectively. Brodner et al. found a 0.7 µg/l cobalt concentration after 5 years[30] and 0.75 µg/l after 10 years.[31] Lazennec reported cobalt levels of 1.55 µg/l and chromium levels of 1.49 µg/l after 9 years.[24] We could not relate cobalt or chromium concentration to periprosthetic radiolucency or prosthetic failure. Although the observed systemic cobalt and chromium levels may inhibit osteoblast proliferation in vitro by as much as 18% (personal data), our patients seemed to tolerate this well. Patients with high ion levels all showed high Harris Hip scores, few or no periprosthetic radiolucencies, and none were revised.

Biologic effects of the submicron metal-on-metal wear particles are under growing investigation and concern.[8, 32, 33] Metal allergy, metal sensitivity, and chromosomal damage are described. Metal sensitivity refers to a type IV delayed-type hypersensitivity reaction and we have reported this phenomenon earlier.[34] The histologic features are described as aseptic lymphocytic vasculitis-associated lesions (ALVAL).[35] In one of our four revised MM patients lymphocyte, eosinophile and macrophage infiltration was described, suggesting possible ALVAL. In the other cases these characteristics were not mentioned, but ALVAL was not that well recognized at the time.

We compared cemented second-generation metal-on-metal total hip arthroplasty to metal-on-polyethylene hip arthroplasty in a randomized controlled trial. At 10 years follow-up both prostheses lead to significant but equal clinical improvement. Cobalt and chromium serum levels were higher in the metal-on-metal patients. We did not observe fewer periprosthetic radiolucencies with the metal-on-metal bearing, nor did we see enhanced prosthetic survivorship. The absence of clinical superiority of the cemented metal-on-metal bearing and the concerns over their biological effects have lead us to favor the cemented metal-on-polyethylene total hip arthroplasty in our clinic.

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Conflict of interest

No competing interests declared.

REFERENCES

1. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg 1992; 74A:849-863.
2. Amstutz HC, Grigoris P. Metal on metal bearings in hip arthroplasty. Clin Orthop Rel Res 1996; 329(Suppl):S11-34.
3. Vail TP, Mina CA, Yergler JD, Pietrobron R. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. Clin Orthop Rel Res 1996; 453:123-131.
4. Beaulé PE, Dorey FJ, LeDuff M, Gruen T, Amstutz HC. Risk factors affecting outcome of metal-on-metal surface arthroplasty of the hip. Clin Orthop Rel Res 2004; 418:87-93.
5. Delaunay CP. Metal-on-metal bearings in cementless primary total hip arthroplasty. J Arthroplasty 2004; 19(Suppl 3):35-40.
6. Schmidt M, Weber H, Schön R. Cobalt chromium molybdenum metal combination for modular hip protheses. Clin Orthop Relat Res 1996; 329(Suppl):S35-47.
7. McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, Grigoris P, Amstutz H. In vivo wear of three types of metal on metal hip prostheses during two decades of use. Clin Orthop Rel Res 1996; 329(Suppl):S128-140.
8. Dumbleton JH, Manley MT. Metal-on-metal total hip replacement: what does the literature say? J Arthroplasty 2005; 20:174-188.
9. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. J Bone Joint Surg 2000; 82A:789-798.
10. Levai JP, Descamps S, Roch G, Boisgard S. Early aseptic loosening of cemented cup in metal-on-metal total hip arthroplasties [Article in French]. Rev Chir Orthop Reparatrice Appar Mot 2006; 92:575-580.
11. Eswaramoorthy V, Moonot P, Kalairajah Y, Biant LC, Field RE. The Metasul metal-on-metal articulation in primary total hip replacement. Clinical and radiological results at ten years. J Bone Joint Surg 2008; 90B:1278-1283.
12. Zijlstra WP, Cheung C, Sietsma MS, Van Raay JJAM, Deutman R. No superiority of cemented metal-on-metal over metal-on-polyethylene total hip arthroplasty in a randomized controlled trial at 5 years follow-up. Orthopedics 2009; 32:479.
13. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fratures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg 1969; 51A:737-755.
14. Söderman P, Malchau H. Is the Harris Hip Score system useful to study the outcome of total hip replacement? Clin Orthop Rel Res 2001; 384:189-197.
15. Gosens T, Hoefnagels NH, de Vet RC, Dhert WJ, van Langelaan EJ, Bulstra SK, Geesink RG. The "Oxford Heup Score": the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. Acta Orthop 2005; 76:204-211.
16. Gruen TA, McNeice GM, Amstutz HC. "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res 1979; 141:17-27.
17. DeLee JG, Charnley J. Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop 1976; 121:20-32.
18. Zicat B, Engh CA, Gokcen E. Patterns of osteolysis around total hip components inserted with and without cement. J Bone Joint Surg 1995; 77A:432-439.
19. Murray DW, Carr AJ, Bulstrode C. Survival analysis of joint replacements. J Bone Joint Surg 1993; 75B:697-704.
20. Dobbs HS. Survivorship of total hip replacements. J Bone Joint Surg 1980; 62B:168-73.
21. Van der Schaaf DB, Deutman R, Mulder TJ. Stanmore total hip replacement: a nine- to ten-year follow-up. J Bone Joint Surg 1988; 70B:45-48.
22. Alsema R, Deutman R, Mulder TJ. Stanmore total hip replacement. A 15- to 16-year clinical and radiographic follow-up. J Bone Joint Surg 1994; 76B:240-244.
23. Gerritsma-Bleeker CL, Deutman R, Mulder TJ, Steinberg JD. The Stanmore total hip replacement. A 22-year follow-up. J Bone Joint Surg 2000; 82B:97-102.
24. Lazennec JY, Boyer P, Poupon J, Rousseau MA, Roy C, Ravaud P, Catonné Y. Outcome and

serum ion determination up to 11 years after implantation of a cemented metal-on-metal hip. Acta Orthop 2009; 80:168-173.
25. Lombardi AV Jr, Mallory TH, Alexiades MM, Cuckler JM, Faris PM, Jaffe KA, Keating EM, Nelson CL Jr, Ranawat CS, Williams J, Wixson R, Hartman JF, Capps SG, Kefauver CA. Short-term results of the M2a taper metal-on-metal articulation. J Arthroplasty 2001; 16(Suppl 1):122-128.
26. Lombardi AV Jr, Mallory TH, Cuckler JM, Williams J, Berend KR, Smith TM. Mid-term results of a polyethylene-free metal-on-metal articulation. J Arthroplasty 2004; 19(Suppl 2):42-47.
27. MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, Leung F. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized controlled trial. Clin Orthop Rel Res 2003; 406:282-296.
28. Jacobs M, Gorab R, Mattingly D, Trick L, Southworth C. Three- to six-year results with the Ultima metal-on-metal hip articulation for primary total hip arthroplasty. J Arthroplasty 2004; 19(Suppl 2):48-53.
29. Medley JB. Tribology of bearing materials. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008:33-38.
30. Brodner W, Bitzan R, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. J Bone Joint Surg 2003; 85A:2168-2173.
31. Grübl A, Marker M, Brodner W, Giurea A, Heinze G, Meisinger V, Zehetgruber H, Kotz R. Long-term follow-up of metal-on-metal total hip replacement. J Orthop Res 2007; 25:841-848.
32. Campbell PA, Takamura KM. Reaction to wear products. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008:133-148.
33. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 2008; 79:734-747.
34. Deutman R, Mulder TJ, Brian R, Nater JP. Metal sensitivity before and after total hip arthroplasty. J Bone Joint Surg 1977; 59A:862-865.
35. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Köster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg 2005; 87A:28-36.

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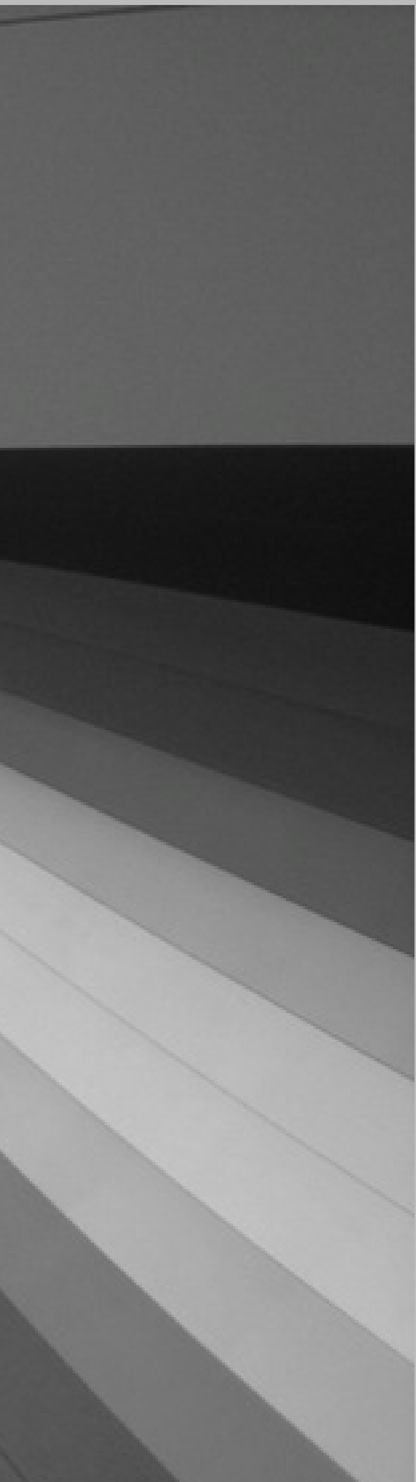

5

Large head metal-on-metal cementless total hip arthroplasty versus 28mm metal-on-polyethylene cementless total hip arthroplasty: design of a randomized controlled trial

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Jos J.A.M. van Raay

BMC Musculoskeletal Disorders
2008;9:136

ABSTRACT

Background

Osteoarthritis of the hip is successfully treated by total hip arthroplasty with metal-on-polyethylene articulation. Polyethylene wear debris can however lead to osteolysis, aseptic loosening and failure of the implant. Large head metal-on-metal total hip arthroplasty may overcome polyethylene wear induced prosthetic failure, but can increase systemic cobalt and chromium ion concentrations. The objective of this study is to compare two cementless total hip arthroplasties: a conventional 28mm metal-on-polyethylene articulation and a large head metal-on-metal articulation. We hypothesize that the latter arthroplasties show less bone density loss and higher serum metal ion concentrations. We expect equal functional scores, greater range of motion, fewer dislocations, fewer periprosthetic radiolucencies and increased survival with the metal-on-metal articulation.

Methods

A randomized controlled trial will be conducted. Patients to be included suffer from non-inflammatory degenerative joint disease of the hip including osteoarthritis, avascular necrosis and traumatic arthritis, are aged between 18 and 80 and are admitted for primary cementless unilateral total hip arthroplasty. Patients in the metal-on-metal group will receive a cementless titanium alloy acetabular component with a cobalt-chromium liner and a cobalt-chromium femoral head varying from 38 to 60mm. Patients in the metal-on-polyethylene group will receive a cementless titanium alloy acetabular component with a polyethylene liner and a 28mm cobalt-chromium femoral head. In both groups the same cementless titanium alloy femoral component is used. We will assess acetabular bone mineral density by dual energy x-ray absorptiometry (DEXA), serum ion concentrations of cobalt, chromium and titanium, self reported functional status (Oxford hip score), physician reported functional status and range of motion (Harris hip score), number of dislocations and prosthetic survival. Measurements will take place preoperatively, perioperatively, and postoperatively (6 weeks, 1 year, 5 years and 10 years).

Discussion

This study has been designed to test whether large head metal-on-metal total hip arthroplasty leads to less periprosthetic bone density loss and higher serum metal ion concentrations compared to conventional 28mm metal-on-polyethylene hip arthroplasty. To our knowledge there is no randomized controlled evidence yet.

BACKGROUND

Painful osteoarthritis of the hip can be successfully treated by total hip arthroplasty (THA). Conventional total hip prostheses consist of a 28mm metal head and a polyethylene cup. Polyethylene wear debris can however lead to osteolysis, bone loss, aseptic loosening and eventually failure of the implant, especially in high demand young patients.[1] Metal-on-metal (MM) total hip arthroplasty is an alternative to overcome polyethylene wear induced prosthetic failure. The MM wear rate is reported to be 20 to 100 times lower than conventional polyethylene wear rates, roughly 6 μm per year.[2] MM wear rate is also influenced by the size of the articulation and its clearance (i.e. the difference between the radius of the head and the shell): larger heads show lower wear rates provided they have a low clearance.[3] Another advantage of larger head sizes seems to be an increased range of motion and a reduced number of dislocations.[4] The main claim of metal-on-metal articulations is a reduction of wear and a subsequent lower incidence of periprosthetic osteolysis. Since osteolysis is implicated in the early phases of prosthetic loosening and failure, it is essential to accurately quantify periprosthetic osteolysis. Conventional radiology is not sensitive and accurate enough to detect small amounts of osteolysis, but dual energy x-ray absorptiometry (DEXA) is able to detect even small defects in the periprosthetic bone in the acetabulum.[5] In spite of the advantages of low wear and fewer dislocations, metal-on-metal hip prostheses increase systemic cobalt and chromium ion concentrations.[6] The long term effects of these ions are unknown, but concerns are hypersensitivity, mutagenicity and carcinogenicity.[7]

The objective of this study is to conduct a randomized controlled trial to compare two cementless total hip arthroplasties: a conventional 28mm metal-on-polyethylene articulation and a metal-on-metal large head articulation. We hypothesize that the large head metal-on-metal arthroplasties show less bone mineral density loss and higher serum metal ion concentrations (primary outcome parameters). We expect equal functional scores, greater range of motion, less dislocations, fewer periprosthetic radiolucencies and increased prosthetic survival with the MM articulation (secondary outcome parameters). The present paper reports on the design of the study.

METHODS

Study design

A randomized controlled trial will be conducted and concealed allocation will be used to allocate patients to either metal-on-polyethylene or metal-on-metal cementless total hip arthroplasty. The randomization procedure is based on sequentially numbered opaque sealed envelopes, produced by an external institution not involved in the selection, clinical care and evaluation of the patients. The study design, procedures and informed consent are approved by the local Medical Ethical Committee (registration number 2005-42). The trial is registered in the Netherlands Trial Registry (NTR1399). Guidelines of the Consort Statement are followed.[8]

Study population

The study will be conducted at the Department of Orthopaedic Surgery of the Martini Hospital, which is a large teaching hospital in the city of Groningen, the Netherlands. Patients to be included suffer from non-inflammatory degenerative joint disease of the hip including osteoarthritis, avascular necrosis and traumatic arthritis, are aged between 18 and 80 and are admitted for primary cementless unilateral THA. Patients with active infection, revision arthroplasty, marked bone loss, and unwillingness or inability to follow instruction are excluded. Participation in the study is voluntary and informed consent is required. The inclusion period is planned from September 2006 to September 2009.

Intervention

Metal-on-metal (MM)
Patients in the metal-on-metal group will receive a metal-on-metal articulation total hip arthroplasty, a cementless plasma sprayed porous coated titanium alloy acetabular component with a cobalt-chromium liner (M2a-Magnum™, Biomet) and a cobalt-chromium femoral head with a carbon concentration between 0.20% and 0.30%. The radial clearances of the articulations vary between 17.5 and 150 micrometers. The head sizes vary from 38 to 60mm, depending on the shell sizes which range from 44 to 66mm. The geometry of the patient determines the largest possible shell size and head size to be implanted.

Metal-on-polyethylene (MP)
Patients in the metal-on-polyethylene group will receive a metal-on-polyethylene total hip arthroplasty, a cementless plasma sprayed porous coated titanium alloy acetabular component (Mallory-Head®, Biomet) with a polyethylene liner (ArCom™, Biomet) and a 28mm cobalt-chromium femoral head with a carbon concentration between 0.20% and 0.30%. In both the MM and MP groups the same cementless femoral component is used: a proximally plasma sprayed porous coated titanium alloy (Ti6Al4V) stem (Mallory-Head®, Biomet).

According to the surgeon's preference, a posterolateral or anterolateral surgical approach in lateral decubitus position is used. Antibiotic prophylaxis with a first-generation cephalosporin will be given preoperatively and during the first twenty-four hours intravenously. All patients will be treated postoperatively following a standardized protocol, in terms of analgesia and mobilization. As prophylaxis against thrombosis, oral anticoagulation by coumarin-derivate is given 6 weeks postoperatively.

Measurements

In this study the following outcome parameters will be assessed: bone densitometry and serum metal ion concentration (primary outcome parameters), self reported functional status, physician reported functional status, range of motion, number of dislocations, radiographic evaluation and prosthetic survival (secondary outcome parameters). Measurements will take place preoperatively, perioperatively, and postoperatively (6 weeks, 1 year, 5 years and 10 years).

Bone densitometry

Bone mineral density (BMD) measurements will be performed using a dual energy x-ray absorptiometry (DEXA) scanner (Hologic Inc., Bedford, Mass., United States) in order to calculate bone density changes around the acetabular component. Four horizontal regions of interest (ROI) are defined, as suggested by Wilkinson.[9] In addition, an extra ROI is defined in the os ilium to serve as control. The manufacturer's metal removal software will be used. The contralateral normal hip will be scanned following a standard manufacturer's protocol to establish BMD in the femoral neck, trochanter, intertrochanteric, total hip and Ward's triangle sites.

Serum metal ion concentration

Serum ion concentrations for cobalt, chromium and titanium will be determined by venous blood sampling. Cobalt and titanium concentrations are analyzed by inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7500 series, Agilent Technologies) and chromium is measured by grafite furnace atomic absorption spectrometry with Zeeman correction (GFAAS; Varian 220Z, Varian Inc.). The patients' sera may also be used to assess cytokine levels and effects of these ions on osteoblast cells.

Perioperative measurements

Surgical approach, surgical time and intra-operative blood loss are recorded. Perioperative complications will be registered, including hip dislocations. The validated Oxford self-rating questionnaire will be used to assess self reported functional status.[10] The validated Harris Hip Score is used to assess patient and physician reported functional status, as well as range of motion.[11, 12]

Radiographic evaluation

During every follow-up visit standard supine anteroposterior (AP) pelvic hip radiographs (with 115% magnification) will be taken. The AP radiographs at 6 weeks will serve as baseline, and will be compared to the X-rays 5 years and 10 years postoperatively. Radiographs are reviewed for presence of femoral radiolucent lines and scored according to the 7 zones described by Gruen et al.[13] Peri-acetabular radiolucencies are assessed according to the three zones of De Lee and Charnley.[14] The scoring will be undertaken by an independent reviewer.

Sample size

It is our hypothesis that large head metal-on-metal arthroplasties will show less bone mineral density loss and higher serum metal ion concentrations compared to the conventional 28mm metal-on-polyethylene articulations. In order to detect a least clinical relevant difference in bone mineral density (BMD) of 0.25 g/cm2 with a standard deviation of 0.4, 41 patients are needed in each group (alpha 0.05, power 0.80). Based on previous work with cemented THA we expect a drop-out rate of 10%, but we also expect conversion to cemented cups if adequate cementless fixation fails. We therefore aim to include 50 patients in each group. Comparable studies also used 50 patients in each group.[15,16] In order to detect a clinical difference of 2.5 µg/liter in serum metal ion concentration with a standard deviation of 1.8, 8 patients per group are needed (alpha 0.05, power 0.80). To compensate for patients withdrawn from the study, (the first) 15 patients will be included in each group. A comparable study used 10 patients in each group.[17]

Statistical analysis

The Statistical Package for the Social Sciences version 14.0 for Windows (SPSS Inc.) will be used. Group comparisons are based on intention-to-treat analysis. Non-parametric tests are used for comparisons of means within groups (Wilcoxon's Signed Ranks Test) and between groups (Mann-Whitney Test) if our expectation of a skewed distribution of Oxford and Harris Hip scores postoperatively is confirmed. Chi-square (Fisher's Exact) tests are employed for analyses of categorical variables. Cumulative implant survival is calculated by Kaplan-Meier time series (Mantel-Cox log rank test). A two-sided p-value of < 0.05 is assumed to be significant.

DISCUSSION

This study has been designed to test whether large head metal-on-metal total hip arthroplasty leads to less periprosthetic bone density loss compared to conventional 28mm metal-on-polyethylene hip arthroplasty. This claim has been put forward by experts, case series and the industry, but to our knowledge there is no randomized controlled evidence. In the short term we will be able to determine whether large head articulations increase clinical range of motion and reduce the number of dislocations. Furthermore, the trial will provide insight in short-term and long-term serum metal ion levels. A related research project will focus on the effects of metal ions on human osteoblast cells in vitro. This is important since the long-term risks of systemic metal ion exposure are unknown. Major pitfalls in orthopaedic surgery research have been the absence of a control group and the lack of randomization. This study overcomes both these drawbacks.

Competing interests

Biomet Netherlands financed the bone densitometry measurements and the serum metal ion analysis. The authors did not receive any reimbursements, fees or salary for performing the study.

Authors' contributions

WPZ designed the study and the data collection protocols, included and reviewed part of the patients, coordinated the trial, wrote the manuscript, and will analyze the data. NB included part of the patients and coordinated the trial. JJAMVR designed the study, included, operated and reviewed part of the patients. All authors read and approved the final manuscript.

Acknowledgements

The study is managed at the Department of Orthopaedic Surgery of the Martini Hospital in Groningen, the Netherlands. Parts of the study are performed at and funded by the Department of Orthopaedic Surgery and the Department of Biomedical Engineering of the University Medical Center Groningen (UMCG), University of Groningen. The study is partly funded by the Anna Fonds and Biomet Netherlands. The Anna Fonds and Biomet have no role in the collection, management, analysis, or interpretation of the data, or the preparation, review or approval of the manuscript.

REFERENCES

1. Schmalzried TP, Jasty M, Harris WH: Periprosthetic bone loss in total hip arthroplasty: polyethylene wear debris and the concept of the effective joint space. J Bone Joint Surg (Am) 1992, 74-A:849-63.
2. McKellop H, Park SH, Chiesa R, Doorn PF, Lu B, Normand P, Grigoris P, Amstutz HC: In vivo wear of metal-on-metal hip prostheses during two decades of use. Clin Orthop Rel Res 1996, 329s:128-40.
3. Dowson D, Hardaker C, Flett M, Isaac GH: A hip joint simulator study of the performance of metal-on-metal joints: Part II: design. J Arthroplasty 2004, 19(8 Suppl 3):124-30.
4. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR: Biomechanics of large femoral heads: what they do and don't do. Clin Orthop Rel Res 2004, 429:102-7.
5. Laursen MB, Nielsen PT, Søballe K: Detection of bony defects around cementless acetabular components in total hip arthroplasty: a DEXA study on 10 human cadavers. Acta Orthop 2006, 77(2):209-17.
6. MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, Leung F: Metal-on-metal versus polyethylene in hip arthroplasty: a randomized controlled trial. Clin Orthop Rel Res 2003, 406:282-296.
7. Dumbleton JH, Manley MT: Metal-on-metal total hip arthroplasty: what does the literature say? J Arthroplasty 2005, 20(2):174-88.
8. Moher D, Schulz KF, Altman DG: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001, 357(9263):1191-1194.
9. Wilkinson JM, Peel NFA, Elson RA, Stockley I, Eastell R: Measuring bone mineral density of the pelvis and proximal femur after total hip arthroplasty. J Bone Joint Surg (Br) 2001, 83-B:283-8.
10. Gosens T, Hoefnagels NH, de Vet RC, Dhert WJ, van Langelaan EJ, Bulstra SK, Geesink RG: The "Oxford Heup Score": the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. Acta Orthop 2005, 76(2):204-11.
11. Harris WH: Traumatic arthritis of the hip after dislocation in acetabular fratures: treatment by mold arthroplasty. J Bone Joint Surg (Am) 1969, 51-A:737-55.
12. Söderman P, Malchau H: Is the Harris Hip Score system useful to study the outcome of total hip replacement? Clin Orthop Rel Res 2001, 384:189-97.
13. Gruen TA, McNeice GM, Amstutz HC: "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res 1979, 141:17-27.
14. DeLee JG, Charnley J: Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop Relat Res 1976, 121:20-32.
15. Laursen MB, Nielsen PT, Søballe K: Bone remodelling around HA-coated acetabular cups: a DEXA study with a 3-year follow-up in a randomised trial. Int Orthop 2007, 31(2):199-204.
16. Kim YH, Yoon SH, Kim JS: Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement. Alumina-on-alumina versus alumina-on-polyethylene articulation. J Bone Joint Surg (Br) 2007, 89-B:174-9.
17. Rasquinha VJ, Ranawat CS, Weiskopf J, Rodriguez JA, Skipor AK, Jacobs JJ: Serum metal levels and bearing surfaces in total hip arthroplasty. J Arthroplasty 2006, 21(6 Suppl 2):47-52.

Waddenzee

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6

Retained periprosthetic acetabular bone density after large femoral head metal-on-metal total hip arthroplasty, short-term results of a randomized trial

Wierd P. Zijlstra
Hugo C. van der Veen
Inge van den Akker-Scheek
Mark J.M. Zee
Sjoerd K. Bulstra
Jos J.A.M. van Raay

Submitted

ABSTRACT

Information on periprosthetic acetabular bone density is lacking for large head metal-on-metal total hip arthroplasties. We aimed to evaluate periprosthetic acetabular bone density, clinical results and serum metal ion levels after large head metal-on-metal total hip arthroplasty . We describe the short term results, at 1 year postoperatively.

We compared cementless large femoral head (mean 48mm) metal-on-metal total hip arthroplasties (M2a-Magnum, Biomet) to cementless 28mm metal-on-polyethylene total hip arthroplasties (Mallory-Head, Biomet) in a randomized clinical trial. Periprosthetic acetabular bone density was analyzed with dual energy x-ray absorptiometry in 70 patients.

After 1 year, bone density decreased (-3.5% to -7.8%) in 3 of 4 regions of interest in metal-on-polyethylene patients, but was retained in all regions in metal-on-metal patients. Bone density preservation was most pronounced superior to the cup (+1% versus -3.7%). Serum cobalt and chromium ion levels were elevated in the metal-on-metal patients (median 1.7, resp. 2.1 µg/L); titanium levels were equal in both groups (5.3-5.7 µg/L). Ion levels were not related to bone density, acetabular inclination or femoral head size. Oxford and Harris hip scores were similar in both groups. The number of early, technical metal-on-metal failures was high (3).

Periprosthetic acetabular bone mass density was retained with large head metal-on-metal total hip arthroplasty, compared to 28mm metal-on-polyethylene arthroplasty. This may support better bone loading and preservation with large head hard-on-hard bearings. Large head metal-on-metal bearings are not forgiving and warrant careful surveillance.

INTRODUCTION

Total hip arthroplasty (THA) is a successful treatment for end-stage osteoarthritis of the hip. THA longevity is hampered by polyethylene wear and subsequent periprosthetic osteolysis.[1] Metal-on-metal (MM) hip arthroplasty is an alternative to overcome polyethylene wear related prosthetic failure. Other alternatives are ceramic and highly-crosslinked polyethylene bearings. Proposed benefits of MM bearings are a reduction of wear, a subsequent lower incidence of periprosthetic osteolysis and eventually improved prosthetic survival.[2] Other conceived advantages are greater range of motion and stability through the use of large femoral heads.[3, 4] Clinical studies of well-positioned contemporary metal-on-metal bearings show acceptable clinical results and acceptable prosthetic survival,[2, 5, 6, 7, 8] but there is increasing concern over unexpected early osteolysis, soft-tissue masses and high failure rates with certain design.[9, 10]

Given the concerns over osteolysis and the widespread use of metal-on-metal total hip arthroplasty, it is striking that little is known about periprosthetic acetabular bone density around these implants. Acetabular bone density has been described around cementless metal-on-polyethylene bearings[11, 12], alumina-on-polyethylene and alumina-on-alumina bearings[13], but all with head sizes up to 28mm. We are unaware of acetabular bone density studies using metal-on-metal bearings, let alone large femoral head hard-on-hard bearings. Therefore, the effects of metal-on-metal bearings, as compared to metal-on-polyethyene, on acetabular bone density are unclear, both in the short and the long term.

Another subject of debate is whether the presence of cobalt and chromium ions alters periprosthetic bone density. It is well known that metal-on-metal hip arthroplasty leads to elevated cobalt and chromium serum ion levels[2, 5, 6, 10], but less is known regarding titanium ions. Systemic cobalt and chromium ion levels correlate strongly with synovial fluid cobalt and chromium ion levels and femoral component wear.[14] Whether serum metal ion levels affect bone density is currently unknown. It can however be assumed from clinical observations and in-vitro studies showing reduced osteoblast proliferation and oxidative stress in the presence of these ions.[10, 15]

The aim of the present study was to set up a randomized clinical trial to evaluate periprosthetic acetabular bone density and serum metal ion levels in large head metal-on-metal cementless total hip arthroplasty, compared to 28mm metal-on-polyethylene cementless total hip arthroplasty. The present paper reports on the short term (1 year) results of the trial.

METHODS

We conducted a randomized controlled trial using concealed allocation. We used sequentially numbered opaque sealed envelopes for randomization. An external institution not involved in the selection, clinical care and evaluation of the patients produced the envelopes. The local Medical Ethical Committee (2005-42) approved the study. The study was registered in the Dutch Trial Registry (NTR1399). The inclusion period ran from September 2006 to November 2008.

Patients

We included consecutive patients suffering from non-inflammatory degenerative joint disease of the hip including osteoarthritis, avascular necrosis and traumatic arthritis. They were aged between 45 and 75 years. We excluded patients with active infection, revision arthroplasty, marked bone loss, and unwillingness or inability to follow instruction. Participation was voluntary and informed consent was required.

Implants

Patients in the metal-on-metal (MM) group received a cementless titanium plasma sprayed porous coated cobalt-chromium-molybdenum alloy acetabular component (M2a-Magnum™, Biomet, Warsaw, IN, USA) and a cobalt-chromium-molybdenum femoral head with a carbon concentration between 0.23% and 0.28%. Diametrical clearances were 150-300µm. Head sizes could vary from 38 to 60mm, depending on the shell sizes ranging from 44 to 66mm.

Patients in the metal-on-polyethylene (MP) group received a cementless plasma sprayed porous coated titanium alloy (Ti6Al4V) acetabular component (Mallory-Head®, Biomet) with a (non-crosslinked) polyethylene liner (ArCom™, Biomet) and a 28mm cobalt-chromium-molybdenum femoral head with a carbon concentration between 0.23% and 0.28%. In both groups the same cementless femoral component was used: a proximally plasma sprayed porous coated titanium alloy (Ti6Al4V) stem (Mallory-Head®, Biomet).

Operative technique

We used a posterolateral or straight lateral surgical approach in lateral decubitus position. Seven orthopaedic surgeons performed the operations. Antibiotic prophylaxis with an intravenous first-generation cephalosporin was given preoperatively and during the first 24 hours postoperatively. All patients were treated postoperatively following a standardized protocol in terms of analgesia and mobilization. Weight bearing was progressively increased as tolerated, crutches were used for six weeks. Low molecular weight heparin was given during 6 weeks.

Bone density

Bone mineral density (BMD) was acquired using a Discovery C (S/N 70141) dual energy x-ray absorptiometry bone densitometer (Hologic Inc, Bedford, MA, USA). The patient's leg was fixed to control rotation. Baseline BMD was measured at the contralateral hip (provided no hip prosthesis was present) and included femoral neck, trochanter, inter-trochanteric, total hip and Ward's triangle sites (Figure 1).

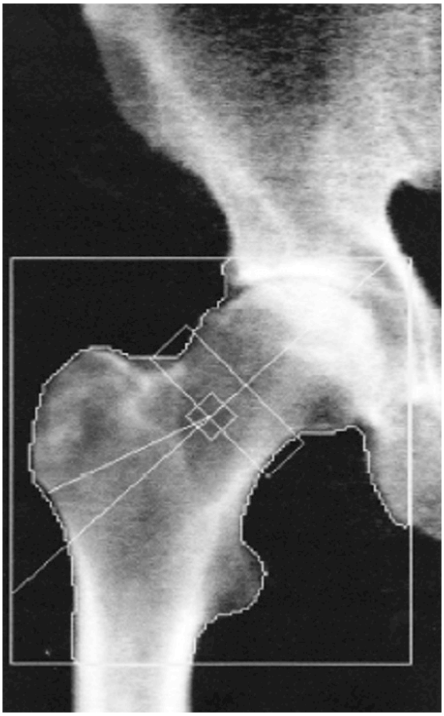

Figure 1. Femoral neck, trochanter, intertrochanteric, total hip and Ward's triangle bone mass density (BMD) measurements with dual energy x-ray absorptiometry (DEXA) of the contralateral hip, serving as baseline measurements six weeks postoperatively. The table is an example of the output derived from the baseline scan.

Region	Area (cm2)	BMC (g)	BMD (g/cm2)	T-score	PR (%)	Z-score	AM (%)
Neck	6.15	4.24	0.689	-1.8	74	-0.6	89
Troch	13.67	9.82	0.718	-0.5	92	-0.1	99
Inter	30.35	32.17	1.060	-0.7	89	-0.2	97
Total	50.18	46.23	0.921	-0.7	89	-0.1	98
Ward's	1.11	0.48	0.430	-2.5	55	-0.7	82

These baseline values were compared to the manufacturer's database so that T and Z values were obtained and presence of osteopenia or osteoporosis was noted. Periprosthetic BMD was analyzed using the manufacturer's metal exclusion software with a template to create four periprosthetic acetabular regions of interest (ROI 1 to 4) according to Wilkinson[11] (Figure 2). We created an extra region at the os ilium ipsilaterally (ROI-6). The regions were manually adjusted to match the anatomy of each patient. The manufacturer's scan comparison software enabled the transfer of the follow-up ROIs onto the baseline ROIs of each patient. Calibration was performed regularly with a phantom; the coefficient of variation was 1%.

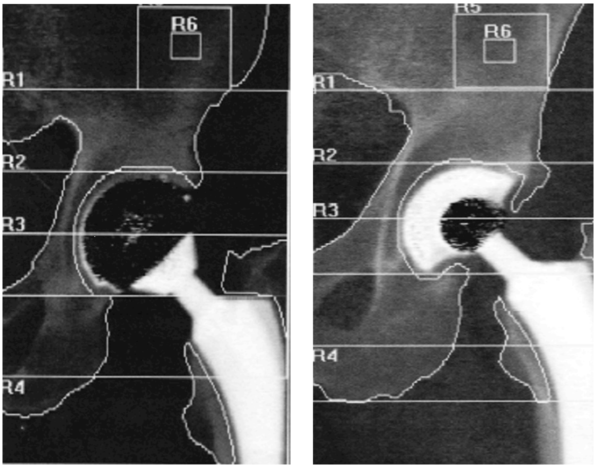

Figure 2. Periprosthetic acetabular regions of interest (ROI) used for the bone mass density (BMD) measurements with dual energy x-ray absorptiometry (DEXA); the table is an example of the output derived from the DEXA scan.

Region	Area (cm2)	BMC (g)	BMD (g/cm2)
GLOBAL	125.27	86.49	0.690
R1	22.69	26.20	1.155
R2	3.40	3.68	1.083
R3	10.53	10.20	0.968
R4	16.33	11.17	0.684
R5	13.07	7.46	0.571
R6	1.41	0.73	0.522
Net	64.57	57.19	0.886

Serum metal ions

Serum cobalt and titanium ion levels were acquired by inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7500 series, Agilent Technologies, Lexington, MA, USA). Chromium ion concentration was measured by graphite furnace atomic absorption spectrometry with Zeeman correction (GFAAS; Varian 220Z, Varian Inc., Lexington, MA, USA). The reference values of our laboratory were <6.8 nmol/l (0.40 µg/l) for cobalt, <48 nmol/l (2.50 µg/l) for chromium and <0.16 µmol/l (7. 66 µg/l) for titanium.

Clinical scores

Oxford questionnaires assessed self reported functional status .[16] Harris Hip Scores measured physician reported functional status.[17] The assessors were orthopaedic surgeons and orthopaedic residents. Assessors and patients were not blinded.

Radiographic evaluation

Supine anteroposterior pelvic hip radiographs were taken preoperatively and at regular intervals postoperatively. The 1 year postoperative radiographs were reviewed by an orthopaedic registrar (MJMZ) and a senior orthopaedic surgeon (JJAMVR). They used the Gruen[18] and DeLee & Charnley[19] classifications for signs of bone resorption, subsidence, osteolysis, interface deterioration, cysts, radiolucencies, reactive line formation, bone densifications, cortical hypertrophy, tip sclerosis and pedestal formation.[20] The acetabular abduction angle (inclination) was measured and periarticular ossifications were noted.

All measurements took place preoperatively and postoperatively at 6 weeks and 1 year. Bone densitometry was not performed preoperatively, the 6 weeks scan served as baseline.

Sample size calculation

In order to detect a least clinical relevant difference in bone mineral density of 0.25 g/cm2 with a standard deviation of 0.4, 41 patients were needed in each group (alpha 0.05, power 0.80). We expected drop-out and conversion to cemented cups if adequate cementless fixation would fail. We therefore aimed to include 50 patients per group. In order to detect a clinical difference of 2.5 µg/liter in serum metal ion concentration with a standard deviation of 1.8, 8 patients per group were needed (alpha 0.05, power 0.80). To compensate for patients withdrawn from the study, (the first) 15 patients were aimed for in each group.

Statistical analysis

We used the Statistical Package for the Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Patient characteristics and outcome measures are presented in means and standard deviations (SD) or in numbers; serum metal ion concentrations are presented in medians and ranges. We tested differences between two groups with independent samples T-tests for continuous variables with normal distribution and Mann Whitney U tests in case of non-normal distribution. Normative distribution was tested with one sample Kolmogorov-Smirnov tests. Fishers Exact test was used for dichotomous variable differences. Comparisons of two means within groups were tested with paired samples T-tests for continuous variables with normal distribution and with Wilcoxon's Signed Ranks tests (two groups) or Friedman tests (three groups) in case of non-normal distributions. Prosthetic survival was calculated by Kaplan-Meier time series (Mantel-Cox log rank test). A p-value of < .05 was considered to be statistically significant.

RESULTS

Patients

We included and randomized a total of 126 patients. Of these, 12 patients were converted intra-operatively to a cemented socket because of inability to fully seat the cementless shell. Five patients decided to postpone or cancel the surgery and 3 did not want to cooperate anymore. Two patients were excluded on the basis of bone deformity. Therefore, a total of 104 patients remained: 54 patients received the 28mm metal-on-polyethylene THA and 50 patients received the metal-on-metal THA. The patients in the two groups were comparable regarding gender, age at operation, and surgical approach (Table 1).

Table 1. Demographics and surgical characteristics in the 28mm metal-on-poly-ethylene (MP) and large femoral head metal-on-metal (MM) groups.

	MP	MM	P-value
	N=54	N=50	
Male/female	25/29	25/25	.844
Age, mean (SD) in years	60 (5)	60 (4)	. 661
Surgical approach (posterolateral / straight lateral)	32/22	32/18	. 689

P-values were calculated by independent-samples T-tests, except male/female ratio and surgical approach; these were calculated by Chi-Square (Fisher's Exact) tests.

Mean femoral head size in the metal-on-metal group was 48.3mm (range 42-56). Surgical complications were encountered in 3 patients: 2 conservatively treated intra-operative fissures (1 MM, 1MP) and one superficial infection (MM). There were no dislocations.

Bone density

Baseline bone density comparison (using the native contralateral hip) of the two prosthetic groups revealed no significant differences (Table 2).

Table 2. Baseline bone mass density (BMD) characteristics in the 28mm metal-on-polyethylene (MP) and large femoral head metal-on-metal (MM) groups.

	MP	MM	P-value
	N=32	N=28	
BMD femoral neck, mean (SD), g/cm2	0.76 (0.12)	0.81 (0.13)	.181
BMD hip total, mean (SD), g/cm2	0.92 (0.12)	0.94 (0.25)	.720
T-score neck, mean (SD)	-1.02 (0.95)	-0. 63 (1.09)	.148
T-score hip total, mean (SD)	-0.48 (0.86)	-0.12 (1.24)	.196
Z-score neck, mean (SD)	0.14 (0.98)	0.55 (1.13)	.136
Z-score hip total, mean (SD)	0.36 (0.97)	0. 66 (1.27)	.313
WHO classification			
N = normal, O = osteopenia, OP = osteoporosis	26 N, 5 O, 1 OP	22 N, 6 O	.559
BMD ROI-6, mean (SD), g/cm2	0. 67 (0.24)	0. 64 (0.26)	.716

All BMD measurements were performed on the contralateral, native hip at six weeks postoperatively. BMD in ROI-6 was measured in the os ilium of the ipsilateral, prosthetic hip. P-values were calculated by independent samples T-tests, except for WHO classification, which was calculated by Chi-Square test.

As another control measure, we analyzed BMD above the prosthetic hip in ROI-6, in the os ilium, distant to the acetabular component. BMD in ROI-6 did not differ between the two prosthetic groups at baseline. BMD in the MM patients was higher than in the MP patients in the medial regions (2 and 3) at six weeks postoperatively (Table 3).

Table 3. Bone mass density (BMD) in the regions of interest (ROI) surrounding the acetabular component of the large femoral head metal-on-metal (MM) and 28mm metal-on-polyethylene (MP) total hip arthroplasties at six weeks and one year postoperatively.

	MP		MM		P-value †
	N=35		N=35		
	Mean (SD)	P ‡	Mean (SD)	P ‡	
ROI-1, 6 wks, g/cm2	1.31 (0.22)		1.43 (0.27)		.051
ROI-1, 1 yr, g/cm2	1.25 (0.22)	.035	1.45 (0.35)	.373	.007
% change	-3.68 (11)		+1.04 (8)		.036
ROI-2, 6 wks, g/cm2	1.15 (0.23)		1.29 (0.30)		.035
ROI-2, 1 yr, g/cm2	1.06 (0.27)	.011	1.22 (0.36)	.057	.038
% change	-7.79 (17)		-5.42 (17)		.569
ROI-3, 6 wks, g/cm2	0.88 (0.19)		1.08 (0.34)		.004
ROI-3, 1 yr, g/cm2	0.83 (0.19)	.005	1.03 (0.37)	.069	.008
% change	-4.57 (10)		-4.48 (13)		.975
ROI-4, 6 wks, g/cm2	0.72 (0.15)		0.79 (0.23)		.152
ROI-4, 1 yr, g/cm2	0.70 (0.16)	.102	0.78 (0.24)	.684	.090
% change	-3.54 (14)		+0.04 (18)		.365

† P-values between groups were calculated by independent samples T-tests.
‡ P-values within groups were calculated by paired samples T-tests and reflect the 6 weeks to 1 year change in BMD.

After 1 year, BMD had decreased in the superior region (ROI-1; -3.7%) and in the two medial regions (2: -7.8%; 3: -4.6%) in the MP patients. In contrast, in the MM patients, BMD had not decreased statistically significantly over time in any region (although numerically in medial regions 2 (-5.4%; p=.057) and 3 (-4.5%; p=.069)). At one year postoperatively, BMD in the MM patients was higher than in the MP patients in all regions except the caudal region 4. Bone density preservation at 1 year was most pronounced superior to the cup (region 1): bone density changed +1% with MM compared to -3.7% with MP (p=.036).

Serum metal ions

Cobalt concentration increased postoperatively in both prosthetic groups. Chromium values did not change in the MP group, but in the MM group they did (Table 4).

Table 4. Serum cobalt, chromium and titanium concentrations (µg/L) in the 28mm metal-on-polyethylene (MP) and large femoral head metal-on-metal (MM) groups, preoperatively and at follow-up.

	MP		MM		P-value †
	N=15		N=14		
	Median	Range	Median	Range	
Cobalt, preoperatively	0.30	0.10-0.50	0.30	0.30-0.60	.114
Cobalt, 6 wks	0.40	0.20-1.10	1.20	0.60-2.70	.000
Cobalt, 1 yr	0.40	0.20-3.71	1.70	0.20-8.51	.002
Chromium, preoperatively	0.50	0.50-0.52	0.50	0.50-0.50	.747
Chromium, 6 wks	0.50	0.50-0.50	0.80	0.50-3.00	.026
Chromium, 1 yr	0.50	0.50-0.80	2.10	0.70-7.09	.000
Titanium, preoperatively	0.96	0.96-4.79	0.96	0.96-6.22	.477
Titanium, 6 wks	8.62	3.83-15.3	9.09	5.27-15.8	.450
Titanium, 1 yr	5.27	0.96-7.66	5.74	3.35-13.4	.145
Cobalt, P-value ‡	.042		.001		
Chromium, P-value ‡	.368		.000		
Titanium, P-value ‡	.000		.000		

†P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Friedman tests (preoperatively versus 6 wks versus 1 yr).

At 6 weeks and 1 yr, cobalt and chromium concentrations were significantly higher in the MM group. Titanium levels increased from pre to postoperatively in both prosthetic groups, were highest at 6 weeks, but did not differ between the groups. We did not find a statistically significant correlation between the 1 year serum metal ion levels and BMD. We could not find a relation between the femoral head size or inclination of the MM acetabular component (mean 52°, SD 7°, range 38-63°) and serum metal ion levels. Patients with steep cups (55° and over) did not show increased ion levels.

Clinical scores

In both the MM and the MP group, Harris and Oxford hip scores improved significantly from preoperatively to 1 year postoperatively (Table 5). At the 1 year postoperative review, there was no difference between the two groups.

Radiographic evaluation

Radiological analysis at one year postoperatively revealed no subsidence, pedestals, bone densification, periprosthetic osteolysis, interface deterioration or reactive line formation. Two patients (1 MM, 1 MP) showed cortical hypertrophy, one (MP) stem tip sclerosis. Two patients displayed bone resorption (2 MP, Gruen 7). One cyst was present in DeLee & Charnley zone 3 (MM) and one radiolucency in Gruen zone 6 (MP). Periarticular ossifications were seen in 16 patients (grade I: 4 MM, 5 MP; grade II: 2 MM, 5 MP).

Table 5. Mean and standard deviation of the Harris Hip (HHS) and Oxford Hip Scores in the 28mm metal-on-polyethylene (MP) and large femoral head metal-on-metal (MM) groups, preoperatively and one year postoperatively.

	MP		MM		P-value †	
	HHS	Oxford	HHS	Oxford		
	N=49*	N=47*	N=44*	N=43*		
Preoperatively	52 (12)	43 (7)	50 (12)	43 (9)	.325	.407
1 yr	88 (11)	28 (15)	89 (7)	26 (13)	.923	.752
P-value‡	.000	.000	.000	.000		

* N is the number of patients at the 1 year follow-up
† P-values between groups were calculated by Mann-Whitney tests.
‡ P-values within groups were calculated by Wilcoxon's Signed Rank tests (preoperatively versus 1 yr).

Analysis of revisions

We revised 3 patients (all MM) within the follow-up period. In the first patient there was a clinically unacceptable leg lengthening postoperatively. This was surgically corrected by repositioning the (same) femoral component. In the second MM patient, we noted a head-cup mismatch on the postoperative x-ray. The femoral head measured 56mm but the acetabular component could only receive a 50mm head in its 56mm shell. We performed the re-operation 2 days later and exchanged the femoral head and taper for the correct size (50mm head). A third MM patient was revised after 2 years and 3 months. The cup was loose. There was no metallosis. Infection was ruled out. An Avantage cup (Biomet, Warsaw, USA) was placed, accepting a 58mm polyethylene bipolar head over a 28mm femoral head. In retrospect, the initially placed 50mm metal head was oversized for the 52mm shell accepting only 46mm heads.

Survival

Cumulative survival at 1 year, with revision for any reason as the endpoint, was 100% for the metal-on-polyethylene THAs (54 patients at risk) and 96% for the metal-on-metal THAs (95%-confidence interval (CI) 90.5-100%; 48 patients at risk). At 3 years, these rates were 100% (24 patients at risk) and 94% (95%-CI 87-100%; 28 patients at risk), respectively. The two survival curves were not statistically different (Mantel-Cox log rank test, p=.069). If the third MM revision as described above is regarded as aseptic loosening, then 1 year metal-on-metal survivorship based on aseptic loosening calculates as 100% and 3 year survivorship as 98% (95%-CI 94-100%; 29 patients at risk; Mantel-Cox log rank test, p=.299).

DISCUSSION

Our study aimed to evaluate periprosthetic acetabular bone density and serum metal ion levels in large head metal-on-metal THA, as compared to 28mm metal-on-polyethylene THA, by means of a randomized clinical trial. Although our data is limited by its short-term follow-up, we found that acetabular bone density was retained with the large head metal-on-metal THA as compared to the 28mm metal-on-polyethylene THA. After 1 year bone density had decreased in 3 of 4 regions of interest in the metal-on-polyethylene patients. In contrast, bone density had remained generally stable in all regions in the metal-on-metal patients, although the two medial regions did show a statistical trend towards bone loss. Bone density preservation was most pronounced superior to the cup. We found no relationship between bone density and serum metal ion levels, in spite of elevated cobalt and chromium levels with the metal-on-metal bearings.

Stress-shielding is a major reason for periprosthetic bone loss after cementless THA. Finite element analysis predicted bone loss medially and bone gain near the prosthetic rim of cementless cups.[21] This has been confirmed clinically with DEXA studies.[12, 13, 14] We also found the largest losses medially (regions 2 and 3). Based on Wolff's law, material properties of the shell and bearing, i.e. thickness and elasticity, can be expected to affect acetabular bone loading and hence bone density. In the past, hard-on-hard bearings (alumina-on-alumina) were compared to polyethylene, but no differences in bone density were found.[13] This study however used thick, small shells (3.8-11mm thick, for 28mm heads). The shells in our study were thinner. The thicknesses of the MM and MP shells were comparable, although the MM pole was thicker (6mm, rim 3mm; MP 3-4mm depending on size). The coating of both shells was identical, but the alloys were different. Titanium alloy (MP shell) is less stiff than cobalt-chromium-molybdenum alloy (modulus of elasticity 114, resp. 214 GPa) and hence one would expect that the Co-Cr-Mo MM shell would show more bone loss. We found the opposite however: the MM bearings preserved acetabular bone better, especially superior to the cup. We speculate that the larger diameter of the MM shell results in lower total stiffness - and hence less stress shielding - than the titanium shell, despite the difference in material stiffness. A less likely possibility is shock absorbance of the polyethylene insert (modulus of elasticity 1.3 GPa[22]), unloading the bone. In spite of these speculations, this is the first study showing the acetabular bone density effects of a large femoral head hard-on-hard bearing.

Serum metal ion levels were not related to bone density. The elevated cobalt and chromium levels with MM bearings were in line with the literature[2, 5, 6] and maximum values were less than mentioned as a risk for metallosis.[14] Titanium levels did not differ between bearings; the highest values seen at 6 weeks possibly reflect that the stem had not established bony ingrowth yet.

The number of early failures with the MM THA was high (3/50). We believe these are related to technical failure and learning curves. In two cases, the femoral head did not match the implanted acetabular liner. These mismatches were technical errors, leading to the wrong clearance and theoretically excessive wear. All cases were early in the learning curve (1st, 2nd and 4th case) of 3 operating surgeons. This illustrates that MM THA is more complex and less forgiving than MP THA. Although we found no evidence for pseudotumors or adverse reactions to metal wear debris yet, we are currently monitoring our patients closely with CT.

Our study has limitations. First of all, our follow-up is only 1 year and thus very short. Efforts are underway to study these patients over the long term to understand if and when differences in acetabular bone density become more or less pronounced. Secondly, we included less than the powered 41x2 patients for the BMD measurements. SD however was less than expected (0.3 versus 0.4), meaning that 35 patients in each group render more than 90% power to detect a 0.25 g/cm2 difference. Thirdly, the MP cup differed from the MM cup with respect to 3 instead of 1 variable: shell alloy, bearing type and head size. This confounds the interpretation of the BMD results, but does represent clinical reality. Lastly, the patients and reviewing surgeons were not blinded. Despite its shortcomings, this is the first randomized trial to report on periprosthetic acetabular bone density in metal-on-metal THAs, and the first to report on large head hard-on-hard THAs.

We conclude that periprosthetic acetabular bone mass density was retained with a large head metal-on-metal total hip arthroplasty, compared to a 28mm metal-on-polyethylene arthroplasty at one year postoperatively. Bone preservation was most pronounced in the area superior to the cup and supports better bone loading with a large head hard-on-hard bearing. The relatively high number of early, technical failures with the large head metal-on-metal bearings illustrate they warrant careful surveillance.

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REFERENCES

1. Purdue PE, Koulouvaris P, Nestor BJ, Sculco TP. 2006. The central role of wear debris in periprosthetic osteolysis. Hosp Spec Surg J 2: 102-113.
2. Dumbleton JH, Manley MT. 2005. Metal-on-metal total hip arthroplasty: what does the literature say? J Arthroplasty 20: 174-188.
3. Zijlstra WP, Van den Akker-Scheek I, Zee MJM, Van Raay JJAM. 2011. No clinical difference between large metal-on-metal total hip arthroplasty and 28mm head total hip arthroplasty? Int Orthop Mar 4.
4. Conroy JL, Whitehouse SL, Graves SE et al. 2008. Risk factors for revision for early dislocation in total hip arthroplasty. J Arthroplasty 23: 867-872.
5. Zijlstra WP, Van Raay JJAM, Bulstra SK, Deutman R. 2010. No superiority of cemented metal-on-metal over metal-on-polyethylene total hip arthroplasty in a randomized controlled trial at 10 years follow-up. Orthopedics 33: 154-161.
6. Grübl A, Marker M, Brodner W et al. 2007. Long-term follow-up of metal-on-metal total hip replacement. J Orthop Res 25: 841-848.
7. Eswaramoorthy V, Moonot P, Kalairajah Y et al. 2008. The Metasul metal-on-metal articulation in primary total hip replacement. Clinical and radiological results at ten years. J Bone Joint Surg Br 90: 1278-1283.
8. Zywiel MG, Sayeed SA, Johnson AJ et al. 2010. Survival of hard-on-hard bearings in total hip arthoplasty, a systematic review. Clin Orthop Relat Res Nov 5, DOI 10.1007/s11999-010-1658-0
9. Park YS, Moon YW, Lim SJ et al. 2005. Early osteolysis following second-generation metal-on-metal hip replacement. J Bone Joint Surg Am 87: 1515-1521.
10. Mabilleau G, Kwon YM, Pandit H et al. 2008. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 79: 734-747.
11. Wilkinson JM, Peel NFA, Elson RA et al. 2001. Measuring bone mineral density of the pelvis and proximal femur after total hip arthroplasty. J Bone Joint Surg Br 83: 283-288.
12. Laursen MB, Nielsen PT, Søballe K. 2007. Bone remodelling around HA-coated acetabular cups: a DEXA study with a 3-year follow-up in a randomised trial. Int Orthop 31: 199-204.
13. Kim YH, Yoon SH, Kim JS. 2007. Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement. Alumina-on-alumina versus alumina-on-polyethylene articulation. J Bone Joint Surg Br 89: 174-179.
14. De Smet K, De Haan R, Calistri A et al. 2008. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg Am 90: 202-208.
15. Zijlstra WP, Bulstra SK, Van Raay JJAM et al. 2011. Cobalt and chromium ions reduce osteoblast-like cell activity in vitro, reduce the OPG to RANKL ratio and induce oxidative stress. J Orthop Res, accepted pending revision.
16. Gosens T, Hoefnagels NH, de Vet RC et al. 2005. The “Oxford Heup Score”: the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. Acta Orthop 76: 204-211.
17. Harris WH. 1969. Traumatic arthritis of the hip after dislocation in acetabular fratures: treatment by mold arthroplasty. J Bone Joint Surg Am 51: 737-755.
18. Gruen TA, McNeice GM, Amstutz HC. 1979. Modes of failure of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res 141: 17-27.
19. DeLee JG, Charnley J. 1976. Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop Relat Res 121: 20-32.
20. Gosens T, Sluimer JC, Kester AD, van Langelaan EJ. 2005. Femoral fit predicts radiologic changes, but not clinical results, in Mallory-Head total hip arthroplasties. Clin Orthop Relat Res 432: 138-147.
21. Levenston ME, Beaupre GS, Schurman DJ, Carter DR. 1993. Computer simulations of stress related bone remodelling around noncemented acetabular components. J Arthroplasty 8: 595-605.
22. Kurtz SM, Mazzucco D, Rimnac CM, Schroeder D. 2006. Anisotropy and oxidative resistance of highly crosslinked UHMWPE after deformation processing by solid-state ram extrusion. Biomaterials 27: 24-34.

Grote Oceaan

Men moat it seil net heger lûke as de mêst

Men moet het zeil niet hoger hijsen dan de mast

7

No clinical difference between large metal-on-metal total hip arthroplasty and 28mm head total hip arthroplasty?

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ABSTRACT

Purpose

We aimed to test the claim of greater range of motion (ROM) with large femoral head metal-on-metal total hip arthroplasty.

Methods

We compared 28mm metal-on-polyethylene (MP) total hip arthroplasty to large femoral head metal-on-metal (MM) total hip arthroplasty in a randomized clinical trial. ROM one year postoperatively was determined in 50 patients. Mean head sizes were 28mm (MP) and 48mm (MM).

Results

After one year, the large head MM group showed more improvement in endorotation (14 degrees) than the 28mm group (7 degrees). There were no significant differences in the absolute values of postoperative endorotation, exorotation, flexion, extension, abduction and abduction.

Conclusions

Absolute postoperative range of motion did not differ between the two groups. The improvement in endorotation was greater after large femoral head metal-on-metal total hip arthroplasty. It is however questionable whether this difference is clinically relevant.

INTRODUCTION

Traditionally, metal-on-polyethylene (MP) total hip arthroplasty (THA) has been using 28mm femoral heads, as larger heads were associated with increased polyethylene wear. With the introduction of highly cross-linked polyethylene 32mm heads have become increasingly popular. Alternative bearings such as ceramic-on-polyethylene, ceramic-on-ceramic and metal-on-metal make even larger femoral heads possible. In hip simulator and biomechanical studies, large femoral heads can increase range of motion (ROM). Crowninshield et al.[1] showed that ROM increased by 30 degrees as the femoral head size increased from 22 to 40mm. Femoral heads over 32 mm provided greater ROM and virtually complete elimination of component-to-component impingement.[2] A 38mm femoral head increased hip ROM compared to the 28mm head and this improvement was 5.3 degrees.[3] All in all, a large head-neck diameter ratio might be the crucial factor for obtaining large ROM.[2, 4]

Whether the results of these preclinical studies also apply in a clinical setting is subject to debate. We found only three clinical studies comparing hip ROM after large femoral head hip arthroplasty to conventional THA. Vail et al.[5] compared hip resurfacing patients to 28 or 32 mm THA patients and found that resurfacing patients had larger ROM postoperatively. This was not a randomized study. Le Duff et al.[6] compared within-subject ROM in 35 patients after hip resurfacing to contralaterally implanted THAs and found no difference. Lavigne et al.[4] showed greater ROM of large femoral head THA over 28mm THA and hip resurfacing, but this study was not randomized. Hence, randomized controlled evidence is still absent.

Aim of our randomized clinical trial was to determine whether large femoral head metal-on-metal total hip arthroplasty has greater ROM at one year postoperatively compared to 28mm metal-on-polyethylene THA.

METHODS

Study design

A randomized controlled trial was conducted. Concealed allocation was used and the randomization procedure was based on sequentially numbered opaque sealed envelopes, produced by an external institution. The study design, procedures and informed consent were approved by the local Medical Ethical Committee (registration number 2005-42). The trial was registered in the Netherlands Trial Registry (NTR1399). Guidelines of the Consort Statement were followed.[7]

Study population

The study was conducted at the Martini Hospital, Groningen, the Netherlands. The patients included suffered from non-inflammatory degenerative joint disease of the hip including osteoarthritis, avascular necrosis and traumatic arthritis, and were aged between 50 and 70. Patients with active infection, revision arthroplasty, marked bone loss, and unwillingness or inability to follow instruction were excluded. Participation in the study was voluntary and informed consent was required.

Interventions

Large femoral head metal-on-metal total hip arthroplasty (MM). Patients in this group received a cementless plasma sprayed porous coated titanium alloy acetabular component with a cobalt-chromium liner (M2a-Magnum™, Biomet) and a cobalt-chromium femoral head with a carbon concentration between 0.20% and 0.30%. Radial clearances varied between 17.5 and 150 micrometers. The head sizes could vary from 38 to 60mm, depending on the shell sizes which ranged from 44 to 66mm. The geometry of the patient determined the largest possible shell size and head size to be implanted.

28mm metal-on-polyethylene total hip arthroplasty (MP). Patients in this group received a cementless plasma sprayed porous coated titanium alloy acetabular component (Mallory-Head®, Biomet) with a polyethylene liner (ArCom™, Biomet) and a 28mm cobalt-chrome femoral head with a carbon concentration between 0.20% and 0.30%. In both the MM and MP groups the same cementless femoral component was used: a proximally plasma sprayed porous coated titanium alloy (Ti6Al4V) stem (Mallory-Head®, Biomet).

A posterolateral or straight lateral surgical approach in lateral decubitus position was used. Six different orthopaedic surgeons performed the operations. Antibiotic prophylaxis with an intravenous first-generation cephalosporin was given preoperatively and during the first twenty-four hours postoperatively. All patients were treated postoperatively following a standardized protocol in terms of analgesia and mobilization. Weight bearing was progressively increased and combined flexion (>90 degrees), adduction and endorotation (posterior approach) / exorotation (straight lateral approach) was prohibited for six weeks. As prophylaxis against thrombosis, low molecular weight heparin was given during 6 weeks.

Measurements

Hip ROM was assessed pre-operatively and one year postoperatively, as part of the Harris Hip Score assessment.[8] The assessors were orthopaedic surgeons and senior orthopaedic registrars. Both the observers and the patients were not blinded. We employed the neutral-zero-method in three planes, i.e. flexion/extension, abduction/adduction, internal/external rotation (supine) using a goniometer. Maximum ROM was defined by the point of soft tissue resistance or pelvic movement on passive motion.

Supine anteroposterior (AP) pelvic hip radiographs (115% magnification) were taken preoperatively and at regular intervals postoperatively. The one year postoperative radiographs were reviewed by an orthopaedic registrar (MJMZ) and a senior orthopaedic surgeon (JJAMVR) using the Gruen[9] and DeLee & Charnley[10] classifications for signs of bone resorption, subsidence, osteolysis, interface deterioration, cysts, radiolucencies, reactive line formation, bone densifications, cortical hypertrophy, tip sclerosis and pedestal formation. We also looked at cup and stem osteointegration, femoral component varus and valgus alignment. We used the definitions published by Gosens et al.[11] The acetabular component abduction angle (inclination) was measured and periarticular ossifications were noted.[12]

Sample size

It was our hypothesis that large head metal-on-metal arthroplasties would show larger ROM compared to the 28mm metal-on-polyethylene articulations. In order to detect a least clinical relevant difference in ROM of 10° with a standard deviation of 10 (SD based on a pilot study), 15 patients were needed in each group (alpha 0.05, power 0.80). We included 25 patients in each group.

Statistical analysis

The Statistical Package for the Social Sciences version 14.0 for Windows (SPSS Inc.) was used. Patient characteristics and outcome measures are presented in means and standard deviations or in numbers. Differences between groups were tested with independent-samples T-tests for continuous variables with normal distribution and Mann Whitney U tests in case of non-normal distribution, and Fishers Exact tests for dichotomous variables. Differences between preoperative and postoperative ROM values were tested with paired-samples T-tests for each group separately. The pre-to-post improvement in ROM was calculated for each patient and the mean difference was tested between the 2 groups using independent-samples T-tests. A p-value of <.05 was considered to be statistically significant.

RESULTS

Preoperatively, both groups were comparable regarding gender, age and ROM in 5 of the 6 ROM measures (Tables 1, 2 and 3). In the MP patients preoperative extension was significantly less than in the MM patients (difference 2°; p=.024). Preoperative flexion, abduction, adduction, endorotation and exorotation were equal (all p-values>.05). Harris hip score was similar (p=.644). Mean head size in the MM patients was 48mm (range 44-54mm). Postoperatively, there were no dislocations.

Table 1. Demographics and surgical characteristics in the 28mm metal-on-polyethylene (MP) and large femoral head metal-on-metal (MM) groups.

	MP	MM	P-value
	N=25	N=25	
Male/female ratio	13/12	13/12	1.000
Age, mean (SD)	61 (5)	60 (5)	.710
Surgical approach (posterolateral / straight lateral)	16/9	15/10	1.000
Femoral head size, mean (SD)	28 (0)	48 (3)	.000

P-values were calculated by independent-samples T-tests, except male/female ratio and surgical approach; these were calculated by Chi-Square (Fisher's Exact) tests.

Table 2. Pre and postoperative hip score and range of motion (in degrees) in the 28mm metal-on-polyethylene (MP) group.

	Preoperative	Postoperative	P-value
	N=25	N=25	
Harris Hip Score, mean (SD)	51 (14)	86 (11)	.000
Flexion, mean (SD)	102 (14)	106 (13)	.148
Extension, mean (SD)	0 (1)	2 (4)	.024
Abduction, mean (SD)	26 (11)	41 (8)	.000
Adduction, mean (SD)	18 (7)	27 (10)	.001
Endorotation, mean (SD)	10 (8)	17 (11)	.001
Exorotation, mean (SD)	21 (12)	29 (11)	.031

P-values were calculated by paired-samples T-tests and refer to the difference between the preoperative and postoperative values

In both groups, the Harris Hip Score increased significantly from preoperatively to one year postoperatively (Tables 2 and 3). From preoperatively to postoperatively, flexion improved significantly in the MM group, but not in the MP group. Extension on the other hand did improve in the MP patients, but not in the MM patients. Abduction, adduction, endo- and exorotation all significantly increased in both groups.

Table 3. Pre and postoperative hip score and range of motion (in degrees) in the large femoral head metal-on-metal (MM) group.

	Preoperative	Postoperative	P-value
	N=25	N=25	
Harris Hip Score, mean (SD)	49 (13)	88 (8)	.000
Flexion, mean (SD)	102 (12)	110 (10)	.020
Extension, mean (SD)	2 (6)	2 (5)	.979
Abduction, mean (SD)	24 (9)	40 (8)	.000
Adduction, mean (SD)	16 (8)	26 (8)	.000
Endorotation, mean (SD)	6 (6)	20 (10)	.000
Exorotation, mean (SD)	21 (12)	28 (10)	.023

P-values were calculated by paired-samples T-tests and refer to the difference between the preoperative and postoperative values

The pre to postoperative improvement in endorotation was significantly larger after the large femoral head MM arthroplasty (14°) compared to the 28mm MP procedure (7°; Table 4). There were no differences between the two groups with respect to improvement of flexion, extension, abduction, adduction or exorotation. The absolute value of postoperative ROM did not differ between groups (all p-values>.05).

Table 4. Preoperative to postoperative improvement in hip score and range of motion (in degrees) in the 28mm metal-on-polyethylene (MP) and large femoral head metal-on-metal (MM) groups.

	MP	MM	P-value
	N=25	N=25	
Harris Hip Score, mean (SD)	35 (16)	39 (13)	.276
Flexion, mean (SD)	5 (15)	8 (16)	.470
Extension, mean (SD)	2 (5)	0 (8)	.229
Abduction, mean (SD)	15 (15)	17 (13)	.673
Adduction, mean (SD)	9 (12)	10 (10)	.702
Endorotation, mean (SD)	7 (10)	14 (13)	.044
Exorotation, mean (SD)	8 (17)	7 (15)	.929

P-values were calculated by independent-samples T-tests and refer to the differences between groups.

Radiological analysis at one year postoperatively revealed that all stems and cups were osteointegrated. We did not observe subsidence, tip sclerosis, pedestals, bone resorption or bone densification. One patient (MP) showed cortical hypertrophy. Evaluation showed no periprosthetic osteolysis, no interface deterioration, no reactive line formation, one cyst in DeLee & Charnley zone 3 (MM) and one radiolucency in Gruen zone 6 (MP). Varus femoral malalignment (>5°) was present in 4 MM patients; no stems were malaligned in valgus. Periarticular ossifications were seen in 12 patients (grade I: 4 MM, 4 MP; grade II: 2 MM, 2 MP). Seventy-six percent of patients had acetabular abduction angles between 40 and 55° (range 24-64°). Mean abduction angle was similar in the MM and the MP patients (resp. 51 (SD 6) and 48° (SD 9); p=.243).

DISCUSSION

Primary goals of THA are pain relief and restoration of mobility. With a rising number of young, active osteoarthritis patients, these mobility demands have become higher and obtaining natural hip motion remains an ultimate goal. Normal healthy hips have a mean 133° flexion, 19° extension, 40° abduction, 30° adduction, 41° endorotation and 39° exorotation.[13] Necessary ROM after THA was suggested to be 120° flexion, 20° abduction and 20° external rotation.[14] After THA mean flexion improved from 82° to 101°, abduction from 10° to 22°, internal rotation from 3° to 16° and external rotation from 16° to 21°.[15] Thus there is a need for improvement in hip ROM after THA.

Hip simulator and biomechanical studies suggest that large femoral heads can lead to greater ROM than 28mm arthroplasties due to a favourable head-neck ratio.[1, 2, 4] To our knowledge this has not been proven clinically in a randomized study. We performed a randomized clinical trial and hypothesized that large femoral head metal-on-metal THAs would yield greater ROM one year postoperatively compared to 28mm metal-on-polyethylene THAs.

The most important findings of our study are: 1) the improvement in endorotation was greater after the large femoral head metal-on-metal arthroplasty (14°) compared to the 28mm arthroplasty (7°); 2) absolute postoperative endorotation and other ROM measures did not differ; 3) there were no differences with respect to improvement of flexion, extension, abduction, adduction and exorotation.

Theoretically, greater endorotation could be caused by a posterolateral surgical approach. In the Cochrane Database[16], the average range of endorotation in extension of the hip was significantly higher with a posterior compared to a direct lateral approach. However, the distribution of both approaches was equal between our two prosthetic groups (MM: 16 posterior, 9 lateral; MP: 15 posterior, 10 lateral). Furthermore, we compared the endorotation improvement in both groups and found no statistically significant difference.

With respect to clinical results, randomized clinical studies on ROM after large and small femoral head THA's are absent as far as we know. Two heterogeneous, non-randomized studies compared hip resurfacing to conventional THA with respect to ROM and found mixed results.[5, 6] One randomized blinded study compared hip resurfacing to THA, but showed no differences in postoperative ROM.[17] A recent cohort study proved that large femoral head arthroplasty had greater total hip ROM compared to 28mm THA.[4] The total arc of rotation was greater in the large femoral head group, but only when measured in prone or legs hanging position. In the supine position, which is the position we used in our study, hip rotations did not differ anymore. This suggests that the improvement in endorotation in our large femoral head patients might have been even greater if measured in prone or legs hanging position. This study lacks randomisation and a description of component positioning.

Component positioning can influence hip ROM. D'Lima et al.[18] found that steeper cups lead to increased flexion, extension and abduction but to decreased adduction and rotation. Endorotation was not influenced by component positioning: it always remained larger than 45 degrees. For maximum ROM and stability with a 28mm head, the authors advised a cup abducted at 45-55°, anteverted at least 15° with 15° of femoral anteversion. Our surgeons generally aim for 40-55° of abduction and this is reflected in the mean radiological abduction angles of 51° and 48° in resp. the MM and MP groups. We did not find any significant correlation between abduction angle and ROM improvement in any direction. We therefore believe it is unlikely that component positioning acted as a large confounder in our study.

Our study has some limitations. Most importantly, our employed clinical method for assessing hip ROM may lack high reliability. In the literature, interobserver reliability of visual (not goniometric) measurement of hip ROM was found to be moderate (intraclass correlation coefficient (ICC) 0.48-0.56)[19]; another study calculated a goniometer endorotation ICC of 0.48.[20] Intraobserver reliability of the goniometer on the other hand proved excellent and similar to that of an electromagnetic tracking system: ICC for endorotation was 0.95 and standard error (SEM) was 2.4°; flexion had the highest SEM (3.9°), concurrent validity was good.[21] Although we did not perform a reliability assessment on our data, we estimate our standard measurement error to be at least 4°. A second limitation is that both the patients and the observers were not blinded. Thirdly, our surgeons used two different approaches (posterolateral and straight lateral). The two prosthetic groups did however not differ with respect to surgical approach. We therefore do not think surgical approach acted as a confounder.

In clinical practice, postoperative improvement of flexion is probably more important than endorotation.[4] However, a greater endorotation of large femoral heads could facilitate the postoperative rehabilitation of patients operated through a posterior approach by allowing more hip motion before dislocation. It could also benefit patients prone to dislocation, for instance those with high physical demand jobs, lower muscular disorders, cognitive dysfunction, dysplasia, previous femoral neck fracture and rheumatoid arthritis.[22] It is questionable whether these benefits may be expected clinically, given the small (7°) endorotation improvement.

Whether or not metal-on-metal is an attractive large femoral head bearing, is debatable given the concerns over long-term biologic effects.[23] If this bearing is chosen, a minimum 46mm head size seems advisable since wear rates decrease with increasing head size (>40mm)[24] and small head sizes have been related to early failures. For ceramic on highly cross-linked polyethylene however, a 32mm head may suffice in terms of range of motion and a 36mm head in terms of wear. Cinotti et al.[3] have shown that 36 and 38mm heads increased ROM compared to 28mm heads, but these sizes added little to the ROM-gain the 32mm head already accomplished. Fisher et al.[25] saw 50% less wear comparing 36mm ceramic to cobalt-chrome heads on highly cross-linked polyethylene. As regards dislocation risk (tested in the lab as impingement), 38+ heads appeared preferable over 28 and 32mm heads in one study[2], but the added value of the 36 and 38mm heads proved negligible over the 32mm head in another study.[3] Thus, increasing femoral head sizes beyond 36mm does probably not bring any additional clinically significant benefit, except for metal-on-metal bearings where a minimum of 46mm seems preferable.

In summary, our study demonstrates that improvement in endorotation is greater after large femoral head metal-on-metal arthroplasty compared to 28mm metal-on-polyethylene THA (14 versus 7°). This is in accordance with hip simulator and biomechanical studies, but has never been shown previously by means of a randomized clinical trial. However, no differences in absolute postoperative endorotation or other ROM measures were found. Whether this difference is therefore clinically relevant is open to discussion, especially since we estimate the standard measurement error to be at least 4°.

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Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR (2004) Biomechanics of large femoral heads: what they do and don't do. Clin Orthop Relat Res 429:102-107
2. Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 20(1):11-19
3. Cinotti G, Lucioli N, Malagoli A, Calderoli C, Cassese F (2010) Do large femoral heads reduce the risks of impingement in total hip arthroplasty with optimal and non-optimal cup positioning? Int Orthop Feb 17 [Epub ahead of print] DOI 10.1007/s00264-010-0954-3
4. Lavigne M, Ganapathi M, Mottard S, Girard J, Vendittoli PA (2010) Range of motion of large head total hip arthroplasty is greater than 28mm total hip arthroplasty or hip resurfacing. Clin Biomech, doi:10.1016/j.clinbiomech.2010.11.001
5. Vail TP, Mina CA, Yergler JD, Pietrobron R (2006) Metal-on-metal hip resurfacing compares favorably with THA at 2 years follow-up. Clin Orthop Rel Res 21:1-9
6. Le Duff MJ, Wisk LE, Amstutz HC (2009) Range of motion after stemmed total hip arthroplasty and hip resurfacing: a clinical study. Bull NYU Hosp Joint Dis 67(2):177-181
7. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357(9263):1191-1194
8. Harris WH (1969) Traumatic arthritis of the hip after dislocation and acetabular fratures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg 51A:737-755
9. Gruen TA, McNeice GM, Amstutz HC (1979) “Modes of failure” of cemented stem-type femoral components: a radiographic analysis of loosening. Clin Orthop Relat Res 141:17-27
10. DeLee JG, Charnley J (1976) Radiological demarcation of cemented sockets in total hip replacement. Clin Orthop Relat Res 121:20-32
11. Gosens T, Sluimer JC, Kester AD, van Langelaan EJ (2005) Femoral fit predicts radiologic changes, but not clinical results, in Mallory-Head total hip arthroplasties. Clin Orthop Relat Res 432:138-147.
12. Brooker AF, Bowerman JW, Robinson RA, Riley LH Jr (1973) Ectopic ossification following total hip replacement. Incidence and a method of classification. J Bone Joint Surg Am 55:1629-1632
13. Svenningsen S, Terjesen T, Auflem M, Berg V (1989) Hip motion related to age and sex. Acta Orthop Scand 60:97-100
14. Johnston RC, Smidt GL (1970) Hip motion measurements for selected activities of daily living. Clin Orthop Relat Res 72:205-215
15. Dela Rosa MA, Silva M, Heisel C, Reich M, Schmalzried TP (2007) Range of motion after total hip resurfacing. Orthopedics 30:352-357.
16. Jolles BM, Bogoch ER (2006) Posterior versus lateral surgical approach for total hip arthroplasty in adults with osteoarthritis. Cochrane Database Syst Rev. 19;3:CD003828
17. Lavigne M, Mottard S, Girard J, Vendittoli PA (2008) Range of motion after hip resurfacing and THA: a single-blind randomized clinical study. Proceedings of the 75th Annual American Academy of Orthopaedic Surgeons Meeting; March 5-9, 2008; San Francisco, California, p. 384-385
18. D'Lima D, Urquhart AG, Buehler KO, Walker RH, Colwell CW (2000) The effect of the orientation of the acetabular and femoral components on the range of motion of the hip at different head-neck ratios. J Bone Joint Surg Am 82:315-321
19. Chevillotte CJ, Ali MH, Trousdale RT, Pagnano MW (2009) Variability in hip range of motion on clinical examination. J Arthroplasty 24(5):693-697
20. Croft PR, Nahit ES, Macfarlane GJ, Silman AJ (1996) Interobserver reliability in measuring flexion, internal rotation and external rotation of the hip using a plurimeter. Ann Rheum Dis 55:320-323
21. Nussbaumer S, Leunig M, Glatthorn GJ, Stauffacher S, Gerber H, Maffiuletti NA (2010) Validity and test-retest reliability of manual goniometers for measuring passive hip range of motion in femoroacetabular impingement patients. BMC Musculoskelet Disord 11:194

22. Lombardi AV, Skeels MD, Berend KR, Adams JB, Franchi OJ (2010) Do large heads enhance stability and restore native anatomy in primary total hip arthroplasty? Clin Orthop Relat Res DOI 10.1007/s11999-010-1605-0
23. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A (2008) Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 79:734-747
24. Medley JB (2008) Tribology of bearing materials. In: Amstutz HC (ed.), Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier: 33-38
25. Fisher J, Lennings L, Galvin A (2006) Wear of highly crosslinked polyethylene against cobalt chrome and ceramic femoral heads. In: Benazzo F, Falez F, Dietrich M (eds), Bioceramics and alternative bearings in joint arthroplasty. Darmstadt: Steinkopff: 185–188

8

Pulsed lavage in cementless total hip arthroplasty reduces the incidence of Brooker grade 3 and 4 heterotopic ossifications

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Submitted

Los Testigos, Venezuela

De see bestiet út drippen

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ABSTRACT

Heterotopic ossification (HO) may cause pain, and can lead to loss of hip motion after total hip arthroplasty (THA). There is evidence that pulsed lavage may lower the incidence of HO formation. We assessed the effect of pulsed lavage on the incidence of HO in 87 male patients after THA.

All patients received a cementless THA through a posterolateral approach. 39 patients were treated with pulsed lavage (index group) and 48 males were treated without pulsed lavage (historical control group, matched on aetiology, gender, surgical approach and type of prosthesis). Both groups followed the same postoperative treatment regimen. HO severity was scored in both groups according to the Brooker classification by three blinded orthopaedic surgeons one year postoperatively.

Good inter-observer agreement (Kappa 0.7) for scoring HO was found. The incidence of HO (51%) in the index group did not differ significantly (p=0.53) from the control group (58%). However, the incidence of clinically relevant HO (Brooker grades 3 and 4) was significantly lower (p=0.04) in the index group (3%) as compared to the control group (17 %).

These results suggest a beneficial effect of pulsed lavage on the incidence of severe heterotopic ossification after cementless THA in male patients.

INTRODUCTION

Heterotopic ossification (HO) is a well-known complication after total hip arthroplasty (THA). The incidence of HO varies from 8% to 90% depending on risk factors and the criteria used.[1, 2] A large meta-analysis of 13 randomized trials, involving 4129 individuals treated with Non Steroid Anti Inflammatory Drugs (NSAIDs) after major hip surgery, reported an overall HO incidence of 37%.[3] Especially advanced stages of HO, Brooker grades 3 and 4, are clinically relevant because of pain and hip function impairment.[4-6]

The exact aetiology of HO remains unclear. Some have suggested that surgical trauma may stimulate primitive mesenchymal cells to differentiate into osteoblastic cells, which form bone.[7, 8] Earlier, Lo and Healy[9] found that non-circulating connective tissue cells with fibroblastic features may cause HO. It seems likely that HO is the result of inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells.

Some risk factors for HO around the hip have been identified; male gender, a lateral surgical approach, uncemented arthroplasty, HO after contralateral hip arthroplasty and revision surgery.[10, 11] Several studies reported beneficial effects of post-operative NSAIDs usage[12] and local radiation therapy[13] in preventing HO formation. However, NSAIDs often cause gastrointestinal side effects, and local radiation may generate higher costs, logistic problems, wound healing disorders and introduces the risk of secondary malignancies.

Pulsed lavage around the hip joint and gluteal muscles may prevent HO formation by washing out the primitive mesenchymal cells. It is inexpensive and has no known side effects. Only one study on the effect of pulsed lavage has been published and suggested no protective effect on HO formation.[1] In this study, however, all patients received lavage; pulsed or manual with a syringe. Aim of the current study was to determine whether pulsed lavage compared to no lavage resulted in less clinically relevant HO formation after cementless THA in male patients.

METHODS

Between May 2003 and February 2006 41 consecutive male patients scheduled for cementless THA were included prospectively. All patients underwent cementless THA through a posterolateral approach because of primary hypertrophic coxarthrosis, and received pulsed lavage during the procedure. Two patients were lost to follow-up. The index group of 39 patients was matched (on aetiology, gender, surgical approach, type of prosthesis and time of follow-up) to a historical control group of 48 patients who received a cementless THA without any form of lavage between March 1993 and December 2001. The local medical ethical committee approved the study design. Informed consent was obtained in all patients. The trial was performed in compliance with the Helsinki Declaration. There were no competing interests.

All patients received a unilateral plasma sprayed porous coated titanium alloy cementless total hip prosthesis with a polyethylene liner (Mallory-Head, Biomet, Warsaw, Indiana, USA) through a standard posterolateral approach. No lavage or irrigation was used in the control group. The index group received pulsed lavage with a total of 1 litre saline at 2 time points; 1: 500 mL after implantation of cup and stem with the hip in dislocated position and 2: 500 mL after reposition. Pulsed lavage was performed with the OptiLavage system (Biomet) in and around the joint and gluteal muscles. After surgery a suction drain was used in all patients routinely. According to protocol no NSAIDs were given postoperatively in both groups. The rehabilitation programme was similar for both groups, and consisted of full weight bearing from the first day after surgery.

HO formation was scored using the Brooker classification on standardized supine anteroposterior pelvic radiographs at time of follow-up.[14] Three blinded orthopaedic surgeons scored all radiographs to assess inter-observer variability.[5] The mode of the 3 observers was used as definitive Brooker score when disagreement in HO rating occurred.

Baseline characteristics of both groups are displayed using descriptive statistics. Differences between groups were tested with Student's T-test or Mann-Whitney U-test in case of non-normal distribution of a parametric variable or non-parametric variable. Interobserver agreement between the 3 observers in scoring of HO formation using the Brooker classification was determined with the kappa statistics. Numbers and percentages of the amount of HO formation in both groups were calculated. Brooker scores were divided into 2 groups: grades 1 and 2 (clinically irrelevant) and grades 3 and 4 (clinically relevant).[4-6] Differences between both groups in clinically irrelevant and clinically relevant Brooker grades were tested with the Fischer's Exact test. All analyses were performed with SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). A p value< 0.05 was considered statistically significant.

RESULTS

Both groups were equal regarding aetiology, gender, surgical approach, type of prosthesis, and time of follow-up. The index group was significantly ($p=0.002$) older with a mean age of 62 years as compared to the control group mean age of 55 years (Table 1).

Table 1. Baseline characteristics for the index and control groups.

	Index	Control
	N=39	N=48
Follow up, months (mean, SD)	12 (7)	15 (8)
Age, years (mean, SD) [a]	62 (9)	55 (10)

[a] p = 0.002

Good inter-observer agreement (K=0.7) for scoring HO formation according to the Brooker classification was found (Table 2). Table 3 shows the distribution of Brooker grades in the index and control group. HO formation was found in 20 out of 39 patients in the index group, and in 28 out of 48 patients in the control group. Total HO incidence percentage (51% and 58%, respectively) did not differ significantly ($p=0.53$) between both groups. However, the index group (1 of 39 patients) had significantly ($p=0.04$) less Brooker grades 3 and 4 HO compared to the control group (8 of 48 patients): 3% versus 17%, respectively.

Table 2. Inter-observer variability for scoring HO formation (Brooker classification), using the □ coefficient for consistency among observers.

O1-O2	0.779	
O1-O3	0.654	
O2-O3	0.734	
Average	0.722	

Table 3. Distribution of the Brooker grades between the index and control groups.

	Brooker0	Brooker1	Brooker2	Brooker3	Brooker4
Index group (N=39)	19	15	4	1	0
Control group (N=48)	20	13	7	6	2

DISCUSSION

Our results demonstrated significantly less severe HO formation (Brooker grades 3 and 4) with the use of pulsed lavage in male patients treated for symptomatic primary hypertrophic coxarthrosis with uncemented THA.

The present study was limited that a historical control group was used as comparison. Patients were not randomized, which may prevent correction for unknown confounding factors that may affect formation of heterotopic bone. Secondly, although our population was homogeneous with respect to gender, aetiology, type of prosthesis, surgical approach, and rehabilitation protocol, the index group was significantly older. Advanced age at surgery is a risk factor for HO after THA .[15] This would suggest that the effect of pulsed lavage is even greater than our results have shown. Thirdly, we only used a radiological outcome at one-year follow-up and no clinical scores were assessed. However, several studies have shown that radiological Brooker grades 3 and 4 correlate positively with clinically relevant HO formation.[4-6] Also a follow-up of one year seems appropriate because HO will be evident and stable in size at 6 weeks postoperatively, while maturation of formed HO takes place up to 6 months after surgery.[16]

A wide range (8-90%) in HO incidence after THA has been described.[1, 11, 15] These differences may depend on the reliability of the HO classification system used. Different systems have been suggested for assessing HO formation. Toom et.al[17] reported high inter-observer reliability for three methods assessing HO formation (Arcq, k=0.9[18]; DeLee, k=0.9[19]; Della Valla, k=0.9[5]). We used the widely accepted and most frequently used Brooker's classification.[20] A recent study showed good inter-observer agreement (k=0.8) for assessing HO formation with the Brooker's classification.[17] We also found good inter-observer agreement (k=0.7) between three experienced blinded orthopaedic surgeons for scoring HO on standard anteroposterior pelvic radiographs. More likely, heterogeneity among studies contributes to the various incidences of HO reported. A recent report on 134 patients who had a cementless hydroxyapatite-coated THA without pharmacologic or radiotherapeutic prophylaxis, showed 67% HO formation.[21] Another randomized study reported 31% HO formation in 97 patients treated with cementless total hip arthroplasty.[22] A systematic overview of 201 studies showed the incidence of any heterotopic bone formation to be 43% after total hip replacement, the incidence of severe HO was 9%.[20] However, information on patient characteristics, use of heterotopic bone formation prophylaxis, NSAID use and details of surgery and follow-up were incompletely reported and generally available for less than one-quarter of the included studies. Risk factors for HO have been recognized and include male sex and posterolateral approach, hypertrophic osteoarthritis.[10, 11] Our study population was selected for these known risk factors, and HO formation was found in 51% of the cases in the index group versus 58% in the control group.

The incidence of clinically relevant HO was 3% in the index group versus 17% in the control group, which was a statistically significant (p=0.04) difference. This suggests a beneficial effect of pulsed lavage on severe HO formation. The exact aetiology of HO formation is still unknown. Some have suggested that mesenchymal pluripotential stem cell release from bone during surgery may act as a stimulus.[23, 24] McCarthy[8] proposed a chain of events in which four factors are important: surgical trauma that leads to hematoma; protein messengers released from traumatized cells or inflammatory cells that arrive at the location of trauma; protein messengers activation of mesenchymal cells to transform into osteoblasts or chondroblasts, and a proper environmental condition that enables HO formation. Pulsed lavage may have the potential to washout mesenchymal pluripotential stem cells and messenger proteins, or to distort the proper environmental condition needed for HO formation. Clinical studies on the effect of pulsed lavage in THA treatment are rare, and only one study reported on pulsed lavage and HO formation.[1] This small and heterogeneous study found no positive effect for pulsed over syringe lavage, but lacked a true control group. A recent Japanese trial on 1000 uncemented THA's through a posterolateral approach reported severe HO formation in only 1% of the cases. A large portion of patients (40%) received NSAIDs postoperatively, and all wounds were irrigated with 1000 mL of saline.[25] Although no pulsatile lavage was used, wound lavage may have had an additional beneficial effect, causing the low incidence of HO.

CONCLUSION

In conclusion our study showed significantly less Brooker grades 3 and 4 heterotopic ossifications after cementless THA in male patients treated with pulsed lavage. This suggests a positive effect of pulsed lavage on preventing clinically relevant HO formation. Future randomized studies may elucidate the role of pulsed lavage better.

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REFERENCES

1. Sneath RJ, Bindi FD, Davies J, Parnell EJ. The effect of pulsed irrigation on the incidence of heterotopic ossification after total hip arthroplasty. J Arthroplasty 2001 Aug;16(5):547-51.
2. Toom A, Haviko T, Rips L. Heterotopic ossification after total hip arthroplasty. Int Orthop 2001;24(6):323-6.
3. Neal BC, Rodgers A, Clark T, Gray H, Reid IR, Dunn L, et al. A systematic survey of 13 randomized trials of non-steroidal anti-inflammatory drugs for the prevention of heterotopic bone formation after major hip surgery. Acta Orthop Scand 2000 Apr;71(2):122-8.
4. Buvanendran A, Kroin JS, Berger RA. Preoperative cyclooxygenase-2 inhibitor treatment reduces the incidence of heterotopic ossification after hip arthroplasty: six-month follow-up. Anesthesiology 2007 Aug;107(2):358-9.
5. Della Valle AG, Ruzo PS, Pavone V, Tolo E, Mintz DN, Salvati EA. Heterotopic ossification after total hip arthroplasty: a critical analysis of the Brooker classification and proposal of a simplified rating system. J Arthroplasty 2002 Oct;17(7):870-5.
6. Kjaersgaard-Andersen P, Ritter MA. Prevention of formation of heterotopic bone after total hip arthroplasty. J Bone Joint Surg Am 1991 Jul;73(6):942-7.
7. Kolbl O, Knelles D, Barthel T, Kraus U, Flentje M, Eulert J. Randomized trial comparing early postoperative irradiation vs. the use of nonsteroidal anti-inflammatory drugs for prevention of heterotopic ossification following prosthetic total hip replacement. Int J Radiat Oncol Biol Phys 1997 Dec 1;39(5):961-6.
8. McCarthy EF, Sundaram M. Heterotopic ossification: a review. Skeletal Radiol 2005 Oct;34(10):609-19.
9. Lo TC, Healy WL. Re-irradiation for prophylaxis of heterotopic ossification after hip surgery. Br J Radiol 2001 Jun;74(882):503-6.
10. Horwitz BR, Rockowitz NL, Goll SR, Booth RE, Jr., Balderston RA, Rothman RH, et al. A prospective randomized comparison of two surgical approaches to total hip arthroplasty. Clin Orthop Relat Res 1993 Jun;(291):154-63.
11. Nollen JG, van Douveren FQ. Ectopic ossification in hip arthroplasty. A retrospective study of predisposing factors in 637 cases. Acta Orthop Scand 1993 Apr;64(2):185-7
12. Knahr K, Salzer M, Eyb R, Frank P, Blauensteiner W. Heterotopic ossification with total hip endoprostheses in various models of thrombosis prophylaxis. J Arthroplasty 1988;3(1):1-8
13. Ayers DC, Evarts CM, Parkinson JR. The prevention of heterotopic ossification in high-risk patients by low-dose radiation therapy after total hip arthroplasty. J Bone Joint Surg Am 1986 Dec;68(9):1423-30.
14. Brooker AF, Bowerman JW, Robinson RA, Riley LH, Jr. Ectopic ossification following total hip replacement. Incidence and a method of classification. J Bone Joint Surg Am 1973 Dec;55(8):1629-32.
15. Kjaersgaard-Andersen P, Sletgard J, Gjerloff C, Lund F. Heterotopic bone formation after noncemented total hip arthroplasty. Location of ectopic bone and the influence of postoperative antiinflammatory treatment. Clin Orthop Relat Res 1990 Mar;(252):156-62.
16. Ritter MA, Vaughan RB. Ectopic ossification after total hip arthroplasty. Predisposing factors, frequency, and effect on results. J Bone Joint Surg Am 1977 Apr;59(3):345-51.
17. Toom A, Fischer K, Martson A, Rips L, Haviko T. Inter-observer reliability in the assessment of heterotopic ossification: proposal of a combined classification. Int Orthop 2005 Jun;29(3):156-9.
18. Arcq M. Die paraartikulären Ossifikationen- eine Komplikation der Totalhüftendoprothese des Hüftgelenks. Arch Orthop Unfall Chir 1973;77:108-31.
19. DeLee J, Ferrari A, Charnley J. Ectopic bone formation following low friction arthroplasty of the hip. Clin Orthop Relat Res 1976 Nov;(121):53-9.
20. Neal B, Gray H, MacMahon S, Dunn L. Incidence of heterotopic bone formation after major hip surgery. ANZ J Surg 2002 Nov;72(11):808-21.
21. Kasetti RJ, Shetty AA, Rand C. Heterotopic ossification after uncemented hydroxyapatite-coated primary total hip arthroplasty. J Arthroplasty 2001 Dec;16(8):1038-42.

22. Rama KR, Vendittoli PA, Ganapathi M, Borgmann R, Roy A, Lavigne M. Heterotopic ossification after surface replacement arthroplasty and total hip arthroplasty: a randomized study. J Arthroplasty 2009 Feb;24(2):256-62.
23. Puzas JE, Evarts CM, Brand JS. The stimulus for bone formation. Hip 1987;25-38.
24. Thomas BJ. Heterotopic bone formation after total hip arthroplasty. Orthop Clin North Am 1992 Apr;23(2):347-58.
25. Higo T, Mawatari M, Shigematsu M, Hotokebuchi T. The incidence of heterotopic ossification after cementless total hip arthroplasty. J Arthroplasty 2006 Sep;21(6):852-6.

El Jadida, Marokko

Troch in lyts lek kin in grut skip sinke

Door een klein lek kan een groot skip zinken

9

Cobalt and chromium ions reduce human osteoblast-like cell activity in vitro, reduce the OPG to RANKL ratio and induce oxidative stress

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ABSTRACT

Metal-on-metal hip arthroplasty is associated with elevated levels of cobalt and chromium ions. The effects of cobalt and chromium ions on cell number, activity, expression of osteoprotegerin (OPG) and receptor activator of nuclear factor kappa B ligand (RANKL) and oxidative stress on human osteoblast-like cells were addressed. Saos-2 cells were supplemented with Co^{2+}, Cr^{3+} or Co^{2+}+Cr^{3+} (1:2) at 0, 1, 10 and 100 µg/L and incubated for 24, 48, 72, and 96 hours. Cell activity was assessed by MTT-assay and cell number by Crystal Violet staining. RNA levels of OPG and RANKL were evaluated using quantitative real-time polymerase chain reaction (qPCR). Compared to controls Co^{2+} reduced cell numbers: at 10 µg/L by 17±8% after 48 hours and at 100 µg/L after 24 hours by 35±8%. Cr^{3+} decreased cell numbers at 10 µg/L after 48 and 72 hours. Co^{2+}+Cr^{3+} combined at 1 µg/L lowered cell numbers after 24 and 96 hours (17±13, resp. 13±4%). The 10 and 100 µg/L concentrations reduced cell numbers significantly after 24, 48 and 96 hours. Cr^{3+} reduced osteoblast activity at 1, 10 and 100 µg/L at all incubation times. The strongest reduction (11±1%) was seen at 100 µg/L after 96 hours. The OPG/RANKL ratio was reduced after 72 hours with almost all Co^{2+} and Cr^{3+} concentrations. After 96 hours, glutathione, superoxide dismutase and catalase levels were indicative for an oxidative stress response in all samples. In conclusion, cobalt and chromium ions reduce human osteoblast activity, reduce OPG/RANKL ratio and lead to oxidative stress.

INTRODUCTION

Total hip arthroplasty (THA) is a well accepted therapy for hip osteoarthritis, with long lasting good clinical results. Survival rates of most THA's are documented at more than 95% over 10 to 15 years. Wear, osteolysis, and loosening have emerged as the dominant concerns among orthopedic hip surgeons. Polyethylene wear particles trigger a foreign body granulomatous reaction, inflammation, and immune reactions leading to the secretion of various bone resorbing agents (cytokines, prostaglandins). This results in peri-prosthetic bone loss, contributing to loosening and failure of the prosthesis.[1] One of the key factors in peri-prosthetic osteolysis is receptor activator of nuclear factor kappaB ligand (RANKL) and strong correlations have been found between its expression and the amount of polyethylene wear debris and the degree of osteolysis.[2] Furthermore, Masui et al. also related the presence of polyethylene to RANKL expression.[3] In general, osteoclastogenesis is largely regulated by receptor activator of nuclear factor kappaB (RANK), RANK-ligand and osteoprotegerin (OPG). RANKL stimulates differentiation of osteoclast precursor cells into mature osteoclasts and is required for osteoclast activity; in fact, RANKL treated mice show increased bone resorbtion. On the other hand, OPG decreases the number of osteoclasts and mice treated with OPG exhibit lowered osteoclast activity and increased bone volume.[4]

In order to avoid polyethylene wear-related loosening and the associated osteolytic problems, metal-on-metal articulation has become popular. Although lower volumetric wear has been shown in the laboratory, metal-on-metal articulation has been associated with higher serum and synovial levels of cobalt and chromium ions compared to metal-on-polyethylene THA articulation. The effects of these ions on bone formation and resorption are still subject to debate. Wang showed that cobalt and chromium ions are not toxic for osteoblasts in concentrations up to 100 ng/ml.[1] Conversely, Fleury et al. recently demonstrated the toxic effects of high concentrations of cobalt (0-10 ppm) and chromium (0-150 ppm) ions on MG-63 osteoblasts in terms of cell number and cellular activity.[5] However, neither of these studies examined the effect of cobalt and chromium ions on the expression of RANKL and OPG by osteoblasts. Metal ions are also known to induce oxidative stress in tissues and cell cultures.[6] On the other hand, in research settings, cobalt ions can also be used as inducer of hypoxia and can induce apoptosis.[7-12]

The aim of the present study was to assess the temporal effect of cobalt and chromium ions on human osteoblast-like cells (Saos-2) in terms of cytotoxicity (cell number and cellular activity), the influence on the expression of bone turnover regulatory proteins RANKL and OPG, and on oxidative stress.

METHODS

Cell culture

Human osteoblast-like cells, originally isolated from a human osteosarcoma (Saos-2, obtained from the American Type Culture Collection (HTB-85)), were maintained in Dulbecco's modified Eagle's medium (DMEM-low glucose,) supplemented with 10% fetal bovine serum (FBS, Invitrogen, Breda, NL), and 1% penicillin/streptomycin (Invitrogen, Breda, NL), and were passaged every 3-5 days. Cells were cultured at 37°C in a humidified 5% CO2-atmosphere. At 70-80% confluence, adherent cells were detached with 0.25% trypsin ethylenediamine-1,2-diaminoethane solution (Trypsin EDTA, Sigma-Aldrich, Zwijndrecht, NL). For the experiments, 1.5 x 104 cells were seeded in 1.5 ml culture medium in 2 cm2 dishes (24-well plates).

Cobalt and chromium ions

$CoCl_2.6H_2O$ (Merck Nederland bv, Amsterdam, NL) and $CrCl_3.6H_2O$ (Sigma-Aldrich, Zwijndrecht, NL) were added in such a way that three solutions at 4 different concentrations were created: cobalt ions at 0, 1, 10 and 100 µg/L, chromium at 0, 1, 10 and 100 µg/L, and cobalt-chromium (1:2) at 0, 1, 10 and 100 µg/L of culture medium. In the latter solutions, twice as much chromium ions as cobalt ions were added, as this reflects the clinical situation with metal-on-metal total hip arthroplasties, where experience suggests that blood chromium concentration is roughly double blood cobalt concentration (1.10 resp. 2.50 µg/L[13]). In addition, we found synovial Cr^{3+} concentration to be more than twice the synovial Co^{2+} concentration in a revision procedure of an uncemented metal-polyethelene total hip arthroplasty with documented wear and loosening (0.60, resp. 1.60 µg/L; personal data). The choice of 1, 10 and 100 µg/L was based on the median serum cobalt concentrations of 0.83 µg/L (maximum 15.6 µg/L) found in previous clinical work on cemented metal-on-metal total hip arthroplasties.[1, 14-16] All solutions were filter-sterilized. Saos-2 cells were incubated with metal ion-containing culture medium in a humidified 5% CO_2-atmosphere at 37°C for 24, 48, 72, and 96 hours. All experiments were performed at least in triplicate.

Cell count

At the end of each incubation period, medium was removed by aspiration, and cells were detached by addition of 0.25% trypsin-EDTA for 3 minutes at 37°C. Cells were isolated, re-suspended and counted using a Bürker-Türk hemocytometer. The mean number of cells for each ion concentration and the incubation period was expressed as percentage of the average number of cells in the negative controls for the corresponding ion and incubation period.

Cellular activity

Cellular activity was assessed with the 3(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT; Sigma-Aldrich, Zwijndrecht, NL). This test is based on the ability of living cells to reduce yellow MTT dye to insoluble purple MTT formazan crystals. At the end of each incubation period, the culture medium was replaced with culture medium supplemented with 0.5 µg/ml MTT and the cells in the 24-well microplates were incubated for an additional 3 hours at 37°C. Liquid was then removed, 2-propanol was added, the plates were shaken for 5 minutes and the OD575 was assessed in a microplate reader (Fluostar Optima, BMG Labtechnologies). Results were expressed as a percentage of the value obtained from the negative control dishes (set at 100%) for the corresponding ion and incubation period.

RNA isolation

Culture medium was removed from the cells, which were immediately lysed using the lysis buffer of an RNA isolation kit (InVisorb spin cell RNA mini kit, InVitek Gmbh, Berlin, Germany). RNA was isolated according to the protocol of the manufacturer. Quantity and purity of the RNA were determined by 260/280 nm absorbance measurements. The RNA samples were subjected to RNase-free DNase digestion to remove any genomic DNA and to agarose gel electrophoresis to assess the intactness of RNA. Complete removal of genomic DNA was verified by PCR. RNA was reverse transcribed using the iScript kit according to the instructions of the manufacturer (Bio-Rad, Veenendaal, NL). The resulting cDNA was 25x diluted, aliquoted and stored at -80°C.

qPCR assays

The qPCR assays were performed in triplicate with qPCR mastermix for SYBR® Green I (Abgene, Westburg, NL)) in 96-well optical plates with primer concentrations of 0.8 µM. Primers for OPG, SOD, Catalase, and RPL13a were designed based on the gene sequences obtained from GeneBank using Perlprimer or Primer-3 software (Freeware and NCBI website, respectively), such that at least one primer from each set was spanning an exon-intron junction (Table 1). Primers for GAPDH were previously described by Emans et al.[17]; the sequences for the primers for RANKL were kindly provided by Dr. Holger Jahr (Erasmus University Medical Center, Rotterdam, NL). Plates were filled using a CAS-1200™ pipetting robot (Corbett Life Science, Sydney, Australia). Five µl of the diluted cDNA was used for each real time quantitative PCR reaction, which was performed in a MyIQ Real-time PCR apparatus (Bio-Rad Inc, Veenendaal, NL). PCR conditions were as follows: 15 min at 95°C, 40 cycles for 15 s at 95°C, and 15 s at 50 - 60°C (gradient), 15 s at 72°C, followed by a melt curve for OPG and RANKL, or 15 min at 95°C, 40 cycles for 15 s at 95°C, and 15 s at 60°C, 15 s at 72°C, followed by a melt curve for SOD and Catalase. Values were normalized to GAPDH (OPG and RANKL), or RPL13a (SOD and Catalase) and the control samples for each incubation time using the 2-ΔΔCt method.[18] The ratio of OPG/RANKL was calculated by dividing the normalized fold expression of both genes within the same sample. Since the experiment was performed in triplicate and the PCR reactions were also performed in triplicate, the statistical analyses were performed on sets of 9 data.

Table 1. PCR primers and their sequences used for real-time PCR. AT is optimal annealing temperature. AT = annealing temperature.

Primer	Sequence 5'-3'	Amplicon size	AT	ref.
		(nucleo-tides)	(°C)	
OPG-forward	GCAGCGGCACATTGGAC	69	60	(Holger Jahr)
OPG-reverse	CCCGGTAAGCTTTCCATCAA			
RANKL-forward	AGAGCGCAGATGGATCCTAA	180	56	
RANKL-reverse	TTCCTTTTGCACAGCTCCTT			
SOD-forward	ACAGCAGGCTGTACCAGTGC	102	60	
SOD-reverse	CACATTGCCCAAGTCTCCAA			
Catalase-forward	CGCAGAAAGCTGATGTCCTG	185	60	
Catalase-reverse	AAAGGCCCCTGCTCCTTTAG			
Gapdh-forward	ACTTTGTGAAGCTCATTTCCTGGTA	107	54	(17)
Gapdh-reverse	GTGGTTTGAGGGCTCTTACTCCTT			
RPL13a-forward	GAGGTATGCTGCCCCACAAA	75	60	
RPL13a-reverse	GTGGGATGCCGTCAAACAC			

Oxidative stress

Oxidative stress was assessed using three different assays. Firstly by assessment of Glutathione (GSH) using a GSH-assay kit (APO/GSH kit, BioVision, ITK diagnostics, Uithoorn, NL). As positive controls in this assay cells were incubated for the respective follow-up periods with 100 μM H_2O_2, added daily. Additionally, oxidative stress was assessed by gene expression of both superoxide dismutase (SOD) and catalase, which was assessed using qPCR as described above. Primers are listed in Table 1.

Statistical analysis

All data were expressed as mean ± standard deviation. For the cell counts, three replicates were used, for the MTT tests, 9 replicates were used, and for the OPG, and

RANKL PCR assays, also 9 replicates were used. For each ion group and incubation time period, statistically significant influences of concentration were tested by univariate analysis of variance (ANOVA), followed by a Bonferroni or Tukey-Kramer analysis for comparing individual groups. Probability less than 0.05 was adopted as the significance criterion. We used the Statistical Package for the Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Cell count

In the presence of increasing concentrations of metal ions, the number of osteoblast-like cells decreased compared to the control samples (Figures 1-3). Cobalt ions at 10 µg/L reduced the number of osteoblast-like cells by 17±8% after 48 hours (p=0.001). At 100 µg/L, the reduction was 12±3% after 48 hours (p=0.010). The strongest reduction was seen at 100 µg/L after 24 hours: 35±8% (p=0.002). Chromium ions decreased the number of osteoblast-like cells at 10 µg/L after 48 and 72 hours (17±7%, resp. 31±2% decline; p<0.001, resp. p=0.001). At 100 µg/L, reductions of 12±9% (p=0.041) and 23±7% (p<0.001) were seen after 48 and 96 hours respectively. Cobalt and chromium combined at 1 µg/L lowered cell numbers after 24 and 96 hours (17±13, resp. 13±4%; p<0.001, resp. p<0.001). The 10 µg/L concentration reduced cell numbers significantly after 24, 48 and 96 hours (p<0.001, p=0.041, p=0.002, resp.). These reductions varied from 14±5% to 35±8%. At 100 µg/L, cobalt+chromium diminished cell numbers after 24, 48, 72 and 96 hours (all p's<0.037).

Cellular Activity

Cellular activity, as measured by the conversion of MTT, showed increased activity with increasing cobalt concentration at 48 hours (p<0.001); see Figures 1-3. Chromium however significantly reduced osteoblast activity at 1, 10 and 100 µg/L at all incubation times (all p's <0.042). The strongest reduction (11±1%) was seen at 100 µg/L after 96 hours (p<0.001). Cobalt and chromium combined increased osteoblast activity after 48 hours at 1 and 10 µg/L (p<0.001, resp. p=0.002).

Figure 1. Osteoblast cell numbers and cell activity after addition of cobalt^{2+} ions in increasing concentrations at consecutive incubation times, expressed as mean ($\pm$SD) percentage relative to the cells without cobalt

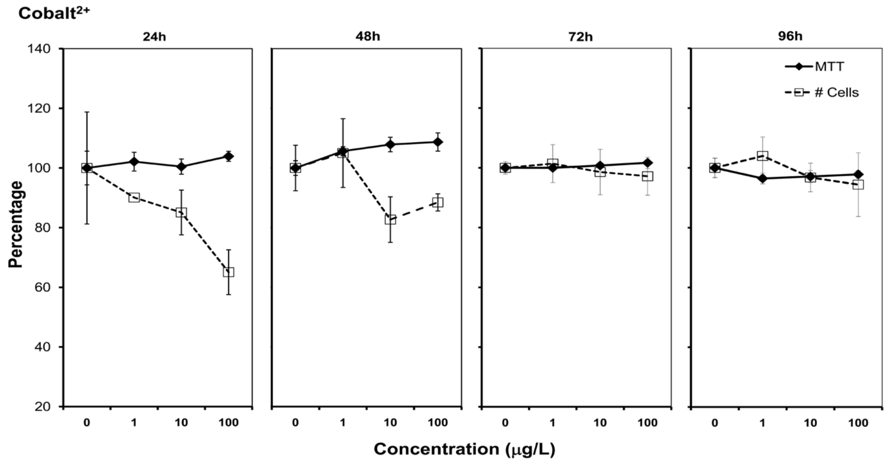


Figure 2. Osteoblast cell numbers and cell activity after addition of chromium^{3+} ions in increasing concentrations at consecutive incubation times, expressed as mean ($\pm$SD) percentage relative to the cells without chromium.

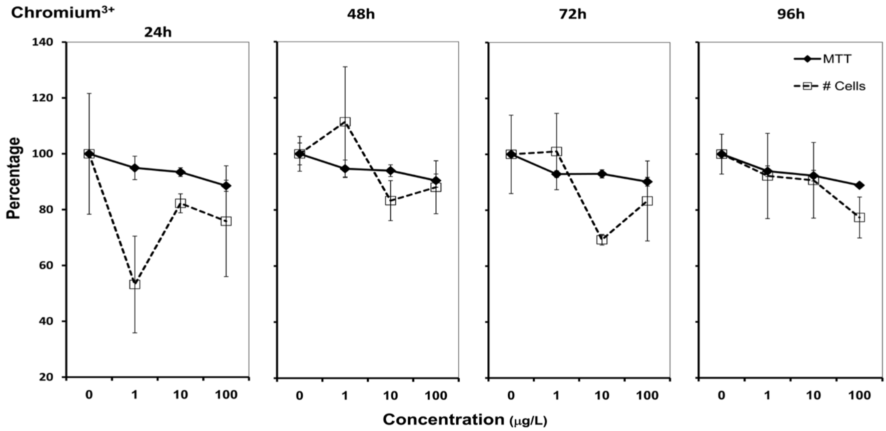
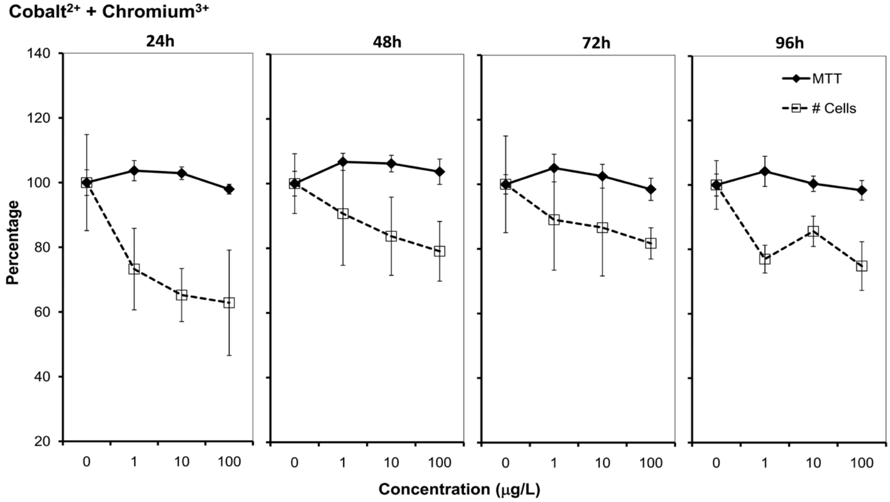


Figure 3. Osteoblast cell numbers and cell activity after addition of cobalt^{2+} plus chromium^{3+} ions in increasing concentrations at consecutive incubation times, expressed as mean (±SD) percentage relative to the cells without cobalt and chromium ions.



RANKL and OPG Expression

The expression of RANKL and OPG was expressed as the ratio of OPG:RANKL in Figure 4. The highest ratios were observed when Cr^{3+} ions were present and with Cobalt + Chromium 100 µg/L at 48 hours. After 72 hours of incubation, the ratio in almost all conditions was significantly lower ($p<0.05$). At 96 hours, the ratio was as low or recovered somewhat; increasing ion concentrations did not seem to affect the ratio.

Oxidative stress

Analysis of glutathione levels in the cells revealed that GSH levels were reduced compared to the control (no additional ions added) in the presence of Co^{2+} at 1 µg/L, 10 µg/L and 100 µg/L at 96h, in the presence of Cr^{3+} ions at 1 µg/L at 48, at 10 µg/L at 48h and 96h and at 100 µg/L at 48 and 96h. Co^{2+} + Cr^{3+} resulted in enhanced GSH concentrations at 1, 10 and 100 µg/L at 24 h. The positive control, incubation with H_2O_2, resulted in significant reduction of GSH concentration ($P<0.05$) at all follow-up moments (Figure 5). The expression of SOD and catalase was hardly changed after 24h for all conditions. SOD expression was reduced with cobalt ions at 100 µg/L at 48h ($P<0.05$). Catalase expression was reduced with chromium ions at 10 µg/L at 48h and 96h and with cobalt + chromium ions at 10 µg/L at 96h ($p<0.05$). After 96 hours, in all samples a definitive trend of oxidative stress response was observed: SOD expression levels were higher than the control, and the catalase expression levels lower (Figure 6).

Figure 4. The ratio of OPG:RANKL mRNA expression has been plotted for the various ion concentrations and incubation times. mRNA levels were assessed using qPCR and calculated using the Livak method (18). The ratio of OPG mRNA/RANKL mRNA was calculated and plotted. Significant differences are given in the text.

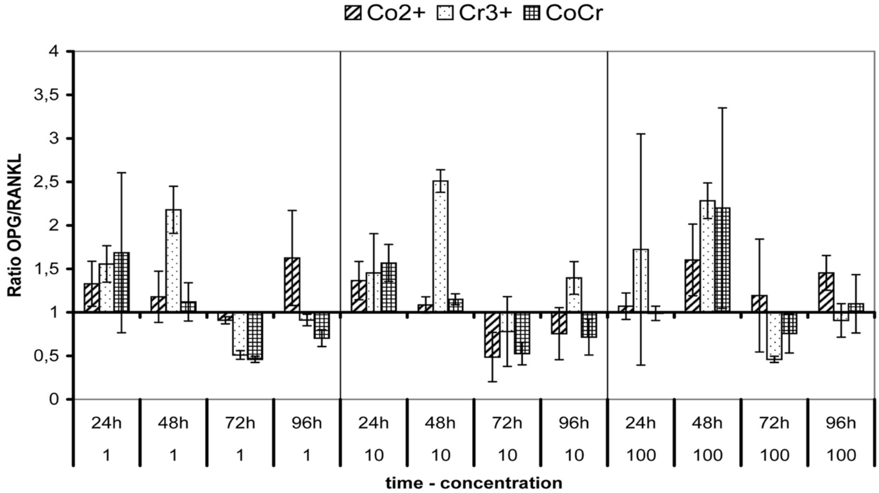
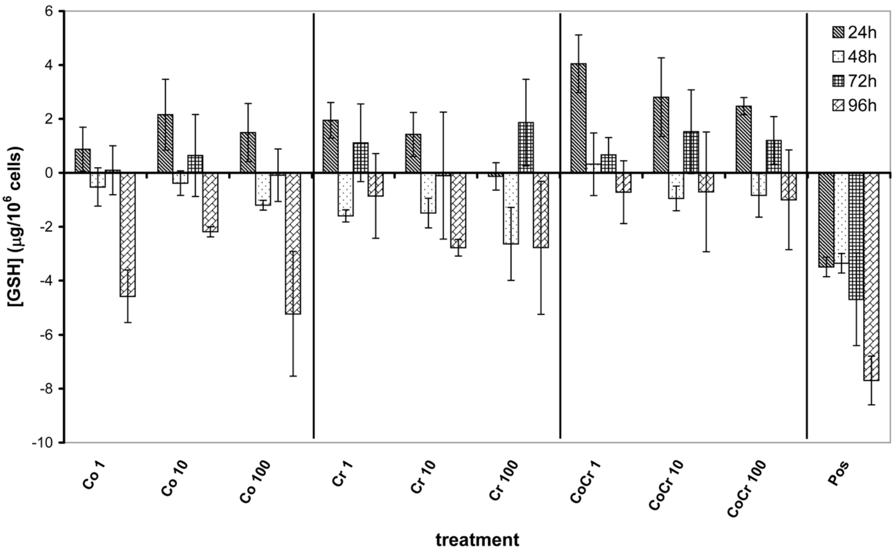


Figure 5. Concentration of GSH plotted against the concentration of Cobalt^{2+}, Chromium^{3+} or Cobalt^{2+} + Chromium^{3+} ions and consecutive incubations times. Significant differences are given in the text.



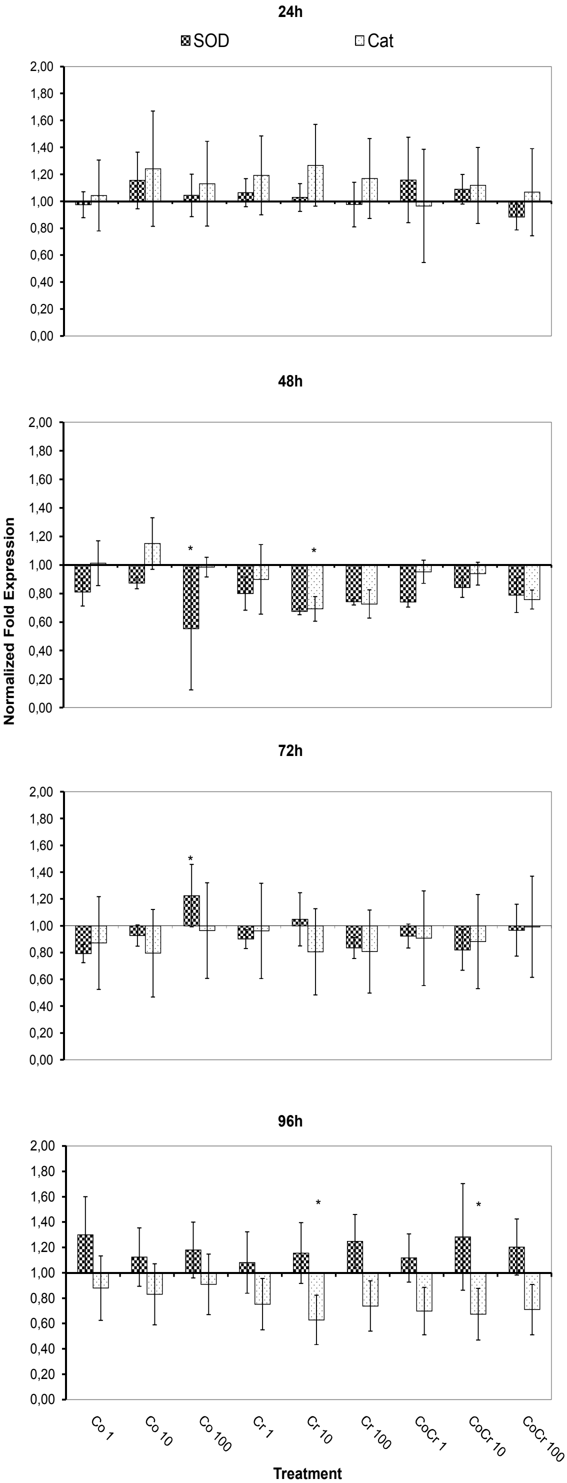


Figure 6. The normalized fold expression of superoxide dismutase (SOD) and catalase (Cat) have been plotted against ion concentration and incubation time. Significant differences are given in the text.

DISCUSSION

We assessed the effects of cobalt and chromium ions on human osteoblast-like cells in relation to cytotoxicity (cell number and cell activity). We also determined the effects on these ions on the expression of bone turnover regulatory proteins RANKL and OPG, as well as on the oxidative stress response. We found that higher ion concentrations were more cytotoxic. Chromium was more toxic than cobalt, yet both ions combined yielded the greatest cell reduction. Cell activity showed a positive relationship to chromium ion levels, thus it decreased when the chromium ion concentration increased. It is remarkable that the cytotoxic effects of the metal ions on cell count, cobalt especially, were strongest in the first 24 hours. It appears that there is some form of adaptive response, for which we have no clear explanation. Sensitization of cells to stimuli is a common phenomenon in cell cultures. In such cases toxicity will only show in the long term. Others[5] also found time (and dose) dependent decreases of osteoblast numbers after addition of cobalt and chromium ions, but used much higher ion concentrations (0-10ppm, i.e. 0-10000μg/L, resp. 0-150ppm, i.e. 150000μg/L). Our results, with clinically relevant concentrations, could indicate that long-term cobalt and chromium ion exposures are not necessarily more harmful than short-term exposure.

Cell activity decreased in a dose-dependent manner after chromium ion addition, but showed no temporal dependance. After exposure to Co^{2+}, activity increased in the first 48 h, then remained fairly stable. Fleury et al.[5] found reduced activity with both Cr^{3+} and Co^{2+}, but used 100 times higher concentrations. It is plausible that during the first 24 to 48 hours after cobalt addition, the osteoblasts up-regulate their activity in an attempt to try to balance their reduction in cell numbers, but plateau after 48 hours.

The oxidative stress assays gave results that were somewhat contradictory. Significant reductions in GSH concentrations were observed after 96 hours with all concentrations of Co^{2+} and at 10 and 100 μg/L of Cr^{3+}, which are in the order of the positive control. The combination of both ions did not reveal any reduction when compared to the control samples. Nevertheless, there were significantly higher levels of GSH in these samples at 24 h follow-up. So after 24 hours also these samples result in a dose-dependent decrease in GSH. The data suggests that cells, in an attempt to protect themselves, began to enhance GSH levels when both ions were added. To our knowledge this has never been described before and warrants further investigation. In contrast, the SOD and catalase mRNA expressions levels were not dependent on the ion dosages of Co^{2+}, Cr^{3+} or $Co^{2+} + Cr^{3+}$. For this we do not have an explanation, other than perhaps SOD and catalase gene expression in these studies were not very much affected by Co^{2+} and Cr^{3+} ions, and apparently do not play a major role in protection of the cells. Furthermore, we found that the OPG to RANKL ratio decreased after 72 hours in almost all conditions, indicating net bone loss. This coincided with an oxidative stress response after 96 hours in all samples.

Although our experiment is an in-vitro study, the tested ion concentrations are clinically relevant. In our own 10-year follow-up study of the cemented Stanmore metal-on-metal total hip prosthesis, serum cobalt and chromium ion concentrations were found ranging from 0.5 to 11 and 0.5 to 9.5 µg/L respectively.[16] A study on failed metal-on-metal bearings showed that there is a very strong correlation between serum cobalt and chromium ion concentration and joint fluid cobalt and chromium ion concentration; the latter was found to be 37 (cobalt) or 47 (chromium) times larger than the serum concentration.[19] This implies that the actual ion concentrations in proximity to the patient's acetabulum and femur could vary between 19 and 447 µg/L.

Our results support available studies describing the detrimental influence of cobalt and chromium ions on osteoblasts (see reference[20] for a short review). Osteoblasts exposed to these ions undergo a dose-dependent reduction in proliferation, show reduced alkaline phosphatase activity, induce oxidation and nitration of proteins and disorganization of the expression of anti-oxidant enzymes[5], release pro-inflammatory cytokines such as interleukin-6 (IL-6) and TNF-alpha and inhibited osteocalcin release and collagen type-I synthesis.[1] On the other hand, Fu et al.[21] found no significant cytotoxicity of Cr^{3+} in rat calvarial osteoblasts and cobalt and chromium ion addition to MG-63 osteoblast-like cells was not associated with interleukin-6 (IL-6) or tumor necrosis factor alpha secretion.[22] Chromium particles however did induce IL-6 synthesis in MG-63 osteoblasts, which in turn may induce osteoclast differentiation.[23] Although different model systems were used in these studies, overall it can be stated that osteoblast function is affected by cobalt and chromium ions and pro-inflammatory cytokines seem to play a major role in this process.

It is not known however, whether bone turnover regulatory proteins RANKL and OPG are involved in the effects of cobalt and chromium ions on osteoblast and osteoclast functioning. We therefore assessed whether cobalt and chromium ions affect RANKL and OPG. Our results show increased OPG to RANKL ratio's 48 hours after addition of Cr^{3+}, followed by reduced ratio's at 72 hours and beyond. Although there was no clear effect of concentration, there was late net bone loss at Co 10 µg/L, Cr 1 µg/L and higher and at Co + Cr 1 µg/L and higher. For clinical practice, this suggests that even in well functioning metal-on-metal implants with systemic cobalt and chromium levels around 1 µg/L, local peri-prosthetic osteolytic reactions may be expected. The oxidative stress response visible after 96 hours further strengthens this assumption. On the other hand, high (100 µg/L) ion concentrations were not more osteolytic than low (1 µg/L) concentrations based on the OPG to RANKL ratios.

Certain limitations apply to our study. We found relatively large standard deviations, especially in the cell count data in the first 24 hours. This is possibly due to the relatively low number of seeded cells in order to culture up to 96 hours, and a low number of replicates. Secondly, we have only studied osteoblast-like cells since these are more easily cultured than osteoclasts. The osteoblasts were studied in-vitro and therefore their natural synovial environment as found in a joint replacement patient was excluded. It is possible that cobalt and chromium ions not only affect osteoblast RANKL, but also lead to TNF-alpha release[24] and hence RANKL expression. TNF-alpha and IL-6 expression was not measured in our study. Furthermore, we have excluded lymphocytes in our experiment. Lymphocytic reactions have been found in retrieved periprosthetic tissues from metal-on-metal arthroplasties[25] ; lymphocytes can also lead to RANKL activation.[26] Tissues retrieved from metal-on-metal arthroplasties showed lower amounts of multinucleated giant cells than expected from metal-on-polyethylene revisions.[27] This suggests that giant cells may play a less important role in peri-prosthetic loosening and failure of metal-on-metal bearings. In contrast, the influence of lymphocytes on RANKL and OPG and their role in metal-on-metal prosthetic failure still requires elucidation.

In conclusion, the main findings of our in vitro study are that cobalt and chromium ions, in clinically relevant concentrations, reduce human osteoblast activity, reduce the OPG to RANKL ratio suggesting osteolysis and lead to oxidative stress.

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REFERENCES

1. Wang, JY, Wicklund, BH, Gustilo, RB, Tsukayama, DT. 1997. Prosthetic metals interfere with the functions of human osteoblast cells in vitro. Clin Orthop Relat Res: 216-226.
2. Holding, CA, Findlay, DM, Stamenkov, R, et al. 2006. The correlation of RANK, RANKL and TNFalpha expression with bone loss volume and polyethylene wear debris around hip implants. Biomaterials 27: 5212-5219.
3. Masui, T, Sakano, S, Hasegawa, Y, et al. 2005. Expression of inflammatory cytokines, RANKL and OPG induced by titanium, cobalt-chromium and polyethylene particles. Biomaterials 26: 1695-1702.
4. Robling, A, Castillo, A, Turner, C. 2006. Biomechanical and molecular regulation of bone remodeling. Annual Review of Biomedical Engineering 8: 455-498.
5. Fleury, C, Petit, A, Mwale, F, et al. 2006. Effect of cobalt and chromium ions on human MG-63 osteoblasts in vitro: morphology, cytotoxicity, and oxidative stress. Biomaterials 27: 3351-3360.
6. Valko, M, Rhodes, CJ, Moncol, J, et al. 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 160: 1-40.
7. Tan, C-B, Gao, M, Xu, W-R, et al. 2009. Protective Effects of Salidroside on Endothelial Cell Apoptosis Induced by Cobalt Chloride. Biological & Pharmaceutical Bulletin 32: 1359-1363.
8. Hara, A, Niwa, M, Aoki, H, et al. 2006. A new model of retinal photoreceptor cell degeneration induced by a chemical hypoxia-mimicking agent, cobalt chloride. Brain Res 1109: 192-200.
9. Zou, W, Zeng, J, Zhuo, M, et al. 2002. Involvement of caspase-3 and p38 mitogen-activated protein kinase in cobalt chloride-induced apoptosis in PC12 cells. J Neurosci Res 67: 837-843.
10. Zou, W, Yan, M, Xu, W, et al. 2001. Cobalt chloride induces PC12 cells apoptosis through reactive oxygen species and accompanied by AP-1 activation. J Neurosci Res 64: 646-653.
11. Yang, SJ, Pyen, J, Lee, I, et al. 2004. Cobalt chloride-induced apoptosis and extracellular signal-regulated protein kinase 1/2 activation in rat C6 glioma cells. J Biochem Mol Biol 37: 480-486.
12. Kim, HJ, Yang, SJ, Kim, YS, Kim, TU. 2003. Cobalt chloride-induced apoptosis and extracellular signal-regulated protein kinase activation in human cervical cancer HeLa cells. J Biochem Mol Biol 36: 468-474.
13. MacDonald, SJ, McCalden, RW, Chess, DG, et al. 2003. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clin Orthop Relat Res: 282-296.
14. Zijlstra, WP, Cheung, J, Sietsma, MS, et al. 2009. No superiority of cemented metal-on-metal vs metal-on-polyethylene THA at 5-year follow-up. Orthopedics 32: 479.
15. Dumbleton, JH, Manley, MT. 2005. Metal-on-Metal total hip replacement: what does the literature say? J Arthroplasty 20: 174-188.
16. Zijlstra, WP, Van Raay, JJ, Bulstra, SK, Deutman, R. 2010. No Superiority of Cemented Metal-on-Metal Over Metal-on-Polyethylene THA in a Randomized Controlled Trial at 10-Year Follow-up. Orthopedics: 154-161.
17. Emans, PJ, Spaapen, F, Surtel, DA, et al. 2007. A novel in vivo model to study endochondral bone formation; HIF-1alpha activation and BMP expression. Bone 40: 409-418.
18. Livak, KJ, Schmittgen, TD. 2001. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods 25: 402-408.
19. De Smet, K, De Haan, R, Calistri, A, et al. 2008. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg Am 90 Suppl 4: 202-208.
20. Mabilleau, G, Kwon, YM, Pandit, H, et al. 2008. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 79: 734-747.
21. Fu, J, Liang, X, Chen, Y, et al. 2008. Oxidative stress as a component of chromium-induced cytotoxicity in rat calvarial osteoblasts. Cell Biol Toxicol 24: 201-212.
22. Hallab, NJ, Vermes, C, Messina, C, et al. 2002. Concentration- and composition-dependent effects of metal ions on human MG-63 osteoblasts. J Biomed Mater Res 60: 420-433.

23. Vermes, C, Chandrasekaran, R, Jacobs, JJ, et al. 2001. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. J Bone Joint Surg Am 83-A: 201-211.
24. Catelas, I, Petit, A, Zukor, DJ, et al. 2003. TNF-alpha secretion and macrophage mortality induced by cobalt and chromium ions in vitro-qualitative analysis of apoptosis. Biomaterials 24: 383-391.
25. Willert, HG, Buchhorn, GH, Fayyazi, A, et al. 2005. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 87: 28-36.
26. Purdue, PE, Koulouvaris, P, Nestor, BJ, Sculco, TP. 2006. The central role of wear debris in periprosthetic osteolysis. HSS J 2: 102-113.
27. Doorn, PF, Campbell, PA, Worrall, J, et al. 1998. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. J Biomed Mater Res 42: 103-111.

La Gomera, Canarische Eilanden

Mei beide fuotten op ’e grûn komst ek gjin stap fierder

Met beide voeten op de grond kom je ook geen stap verder

10

General discussion and conclusions

GENERAL DISCUSSION

The general aim of this thesis is **to determine the clinical outcome and bone implications of metal-on-metal total hip arthroplasty.** We formulated four research objectives. We will discuss the research results of each of these objectives.

1. To determine the mid and long term clinical outcome of cemented 28mm metal-on-metal THA in comparison with metal-on-polyethylene THA

We studied the clinical outcome of a cemented 28mm metal-on-metal THA (Stanmore M2A; Biomet, Warsaw, Indiana, USA). We performed a prospective randomized trial and used a cemented 28mm metal-on-polyethylene THA (Stanmore; Biomet) as a comparison. We have been using the latter prosthesis in our clinic since 1975.[1, 2, 3] We found that both articulations led to significant clinical improvements. At both 5-year (Chapter 3) and 10-year follow-up (Chapter 4), Harris and Oxford hip scores did not differ between the two groups. Long-term periprosthetic radiolucent lines were mainly seen medially to the acetabular component. The frequency of radiolucencies did not differ statistically between the two articulations. Focal osteolysis was absent. Five-year prosthetic survival, with revision for any reason as the endpoint, was 97% (3 revisions) for the metal-on-metal articulation and 99% (1 revision) for the metal-on-polyethylene articulation, with no significant difference. Ten-year survival was 95.5% (4 revisions) for the metal-on-metal articulation and 96.8% for the metal-on-polyethylene articulation (2 revisions), with no statistically significant difference.

Our clinical results and survival are comparable to, or even better than other cemented metal-on-metal THA series.[4, 5, 6, 7] Two of these groups discontinued using the cemented metal-on-metal bearing (because of progressive radiolucencies or inferior survival). Based on clinical results, radiological performance and prosthetic survival, the cemented 28mm metal-on-metal THA in our series performed quite well. A 13-year follow-up of a 28mm metal-on-metal THA also showed a similar overall survival (94%).[8] Recently, the Australian Joint Registry confirmed our clinical results by finding that <28mm metal-on-metal bearings performed no different from other <28mm bearings and had a cumulative survival of 94.9% at nine years.[9] We did not find any specific metal-on-metal bearing related adverse events, apart from one patient where lymphocyte, eosinophile and macrophage infiltration was described at revision, suggesting possible ALVAL.[10] Nonetheless, we favor the cemented metal-on-polyethylene THA in our clinic, given the absence of clinical superiority of the cemented metal-on-metal bearing and the concerns over possible biological effects. To the existing literature, our study has added the only published randomized trial on metal-on-metal THA with 10 years follow-up. A recent meta-analysis of all randomized trials reached exactly the same conclusion: no proven clinical advantages of metal-on-metal over metal-on-polyethylene THA.[11]

Future research could focus on the 15-year clinical outcomes of our patient group and use a more sensitive method for assessing the periprosthetic area, for instance CT or MRI, and correlate this with serum cobalt and chromium ion levels.

2. To determine the short term clinical outcome and periprosthetic bone implications of cementless large femoral head metal-on-metal THA in comparison with metal-on-polyethylene THA

We designed a randomized clinical trial to assess clinical outcome and periprosthetic bone density changes around the acetabular component of a cementless large femoral head metal-on-metal THA (M2A Magnum; Biomet) (Chapter 5). We used a cementless 28mm metal-on-polyethylene THA as a comparison (Mallory-Head Ringlock with Arcom polyethylene; Biomet). We used the same cementless stem in both groups (Mallory-Head; Biomet). We selected dual energy x-ray absorptiometry (DEXA) because it was sensitive to osteolysis,[12] had low radiation exposure and was cost-effective. We measured cobalt, chromium and titanium ion levels in the serum in part of the patients.

At one year postoperatively, we found that acetabular bone density was retained with the large head metal-on-metal THA (Chapter 6). Bone density had decreased over the year in 3 of 4 regions of interest in the metal-on-polyethylene patients, but had remained statistically stable in all regions in the metal-on-metal patients. Bone density preservation was most pronounced superior to the cup. Bone density was not related to serum metal ion levels, in spite of elevated cobalt and chromium levels with the metal-on-metal bearings.

Our bone density findings at one year are more related to biomechanical phenomena than wear-particle induced phenomena, which is to be expected. The finding of preservation of acetabular bone with a large head hard-on-hard bearing is novel, as far as we know. In the past, hard-on-hard bearings (alumina-on-alumina) were compared to polyethylene, but no differences in bone density were found.[13] Stress-shielding is a major reason for periprosthetic bone loss after cementless THA. Thickness and elasticity of the shell and bearing can be expected to affect acetabular bone loading and hence bone density, based on Wolff's law. The thicknesses of both shells were roughly comparable (the pole of the metal-metal shell was thicker), but the alloys were different. Titanium alloy (metal-on-polyethylene shell) is less stiff than cobalt-chromium-molybdenum alloy (metal-on-metal shell) and hence one would expect that the Co-Cr-Mo shell would show more bone loss. We found the opposite however: the metal-on-metal bearings retained acetabular bone, especially superior to the cup. We speculate that the larger diameter of the metal-on-metal shell results in lower total stiffness - and hence less stress shielding - than the titanium shell, despite the difference in material stiffness.

It will be essential to see what happens to the acetabular bone density after 5 or 10 years, when the effects of metal wear particles and ions start to take effect. At the start of our thesis project we hypothesized that the lower wear of the metal-on-metal bearing would lead to less periprosthetic bone loss in the long term. With the abundance of information on metal-on-metal bearings over the last 5 years, and the knowledge gained from our in-vitro studies, we will have to alter our hypothesis. If elevated metal ion levels around the metal-on-metal bearing indeed reduce osteoblast activity and give rise to osteolysis via the RANKL/OPG pathway, than we should be able to find more periprosthetic bone loss by bone densitometry in the future.

To date, however, our clinical data do not demonstrate negative effects on periprosthetic bone of a metal-on-metal THA or of elevated metal ion levels. Our cemented 28mm metal-on-metal THAs did not show focal osteolysis or more periprosthetic radiolucencies at 5 or 10 years follow-up, compared to metal-on-polyethylene THAs; we did find ALVAL in one revision case. The one year conventional x-rays and DEXA-scans do not indicate negative bone implications of the large femoral head metal-on-metal THAs. We have not observed pseudotumors, nor complaints suggesting pseudotumors as of yet. However, our follow-up is of course short and we are aware that metal-on-metal bearings >32mm have an increased failure rate after 2 years, especially in younger patients and females.[9] For our prosthesis specifically, the cumulative percent revision is 2.2 at 3 years, which is significantly lower than the ASR (5.9), and comparable to the <28mm metal-on-polyethylene THA (2.5) and the >28mm ceramic-on-ceramic THA (2.3). Others have warned for high failure rates of hybrid large femoral head metal-on-metal bearings, blaming the trunion-head interface.[14] Some implants have indeed shown high cobalt ion levels potentially originating from the junction between the stem and the adaptor sleeve, but the Biomet large metal-on-metal implant we used showed the lowest ion levels in a comparative study, likely because of its titanium sleeve.[15] Silent, subclinical abnormalities such as fluid collections may be more frequently visible with MRI around metal-on-metal joints, but the number of MRI abnormalities did not differ significantly with metal-on-polyethylene bearings.[16] All in all, we are monitoring our patients closely and will report on the 5-year DEXA data and ion levels in the future. It may be worth performing metal ion levels and CT or MRI in all patients then.

With respect to metal ion levels, we found elevated serum cobalt and chromium ion levels with the large head metal-on-metal bearing (median 1.7 and 2.1 μg/L, respectively). These were in line with the literature[17, 18, 19] and maximum values (cobalt 8.5, chromium 7.1 μg/L) were less than mentioned as a risk for metallosis.[20] Titanium levels did not differ between bearings. We found no relation between metal ion levels and bone density. Perhaps the ion levels were too low to induce bone density changes, or the number of samples was insufficient since ion levels were not determined in all patients (the study was powered to detect a 2.5 µg/L difference between both bearings and for this only 8 patients in each group were needed). In our 5 and 10-year follow-up of the 28mm metal-on-metal THA, serum cobalt and chromium ion levels were elevated too (median 1.1 and 1.0 µg/L, respectively). Again, higher ion levels (max. 11 µg/L) were not related to radiographic changes and did not lead to adverse events in patients.

A major task for future research is to establish predictive cut-offs for cobalt and chromium ion levels indicating possible prosthetic failure. One study proved that cobalt levels > 19 µg/L predicted metallosis at revision.[20] The definition of a statistical outlier was used to define a 7 µg/L limit, resulting in 90% specificity but only 50% sensitivity for metal-on-metal hip failure.[21] Recently, a 120 nmol/L cobalt threshold (7 µg/L) showed 83% sensitivity and 52% specificity for hybrid metal-on-metal THA failure.[14] The Dutch Orthopaedic Society put forward 5 µg/L as the serum cobalt level that necessitates further investigations with CT, ultrasound or MRI.[22] The American and Australian Orthopaedic Associations choose not to define exact 'concern' tresholds, but suggest the results should the interpreted in the light of clinical findings and imaging studies.[22, 23] Making the decision to revise a metal-on-metal bearings solely on serum metal ion levels is not evidence-based. The decision when to revise is complex. Revision can be considered in the presence of (a combination of) lysis, loosening, pseudotumour, pain, poor functional score, head size <44mm in resurfacing, >32mm head size in THA, young patients, a malaligned cup (>55degrees inclination), the ASR design, raised serum cobalt or chromium levels. For the practicing orthopaedic surgeon, an algorithm would be most helpful, and the prognostic capabilities of such an algorithm should be focus of further research.

3. To assess the effect of large femoral head THA on range of motion and to study heterotopic ossification as a factor that can compromise range of motion

We studied clinical range of motion (ROM) after large femoral head metal-on-metal THA (Chapter 7). Again, we used a 28mm metal-on-polyethylene THA for comparison, in a randomized trial. Hip simulator and biomechanical studies suggest that large femoral heads can lead to greater ROM,[25, 26] but this had not been shown clinically in a randomized study. In our trial, we found that improvement in endorotation is greater after large (48mm) femoral head total hip arthroplasty, compared to 28mm THA (14 versus 7°). However, no differences in absolute postoperative endorotation or other ROM measures (flexion, extension, abduction or adduction) were found.

Whether this small difference in endorotation (7°) is clinically relevant is open to discussion. We estimate our measurement error to be around 4° based on our clinical method of ROM measurements. With a more sophisticated ROM measurement system, a recent cohort study proved that large femoral head arthroplasty had greater total hip ROM compared to 28mm THA.[27] The total arc of rotation was greater in the large femoral head group, except for the supine position, which is the position we used in our study.

Large femoral heads may prevent hip dislocation, however. This is due to greater jump distance, greater range of impingement free motion and greater vertical travel distance in hip simulations.[25] None of our trial patients dislocated their THA postoperatively. Thus we found no evidence for dislocation prevention with large femoral heads. However, our study was not designed, and thus underpowered, to measure a possible difference in dislocation rate. Data from the 2010 Australian Joint Registry show less revisions for dislocation with >28mm heads (0.4%) compared to <28mm heads (1.4%), irrespective of bearing material (Marel 2011, personal communication). In a critical review of the literature, the Dutch Orthopaedic Association's THA Working Group noted that 32mm femoral heads reduced the number of posterior dislocations compared to 28mm heads, but with a trade-off: more wear at 10 years with traditional polyethylene.[28] Whether this is also true for cross-linked polyethylene remains to be seen: femoral heads >32mm reduced dislocations compared to 22, 28 and 32mm heads, but clinical follow-up was less than 5 years and hence possible trade-offs (edge-wear) are more uncertain.[28]

The question is whether femoral heads greater than 36mm bring any additional clinical benefits. It was shown that 36 and 38mm heads can increase ROM compared to 28mm heads, but these sizes added little to the ROM-gain the 32mm head already accomplished.[29] Head sizes over 40mm improve fluid-film lubrication and hence wear characteristics.[30] Nonetheless, greater than 32mm metal-on-metal THAs are at increased risk of revision compared to <28mm and 30-32mm heads.[9] This supports the increased failure rate of large femoral head metal-on-metal THAs in Zwolle, presented recently at the Dutch Orthopaedic Society meeting and in the UK.[14]

Severe heterotopic ossifications (HO) may compromise hip range of motion. We tend to use peroperative pulsed lavage in our clinic if the a-priori risk for HO is high (for instance with male gender, cementless THA, previous HO, lateral approach, revision surgery). We studied the incidence of HO after cementless THA, with and without peroperative pulsed lavage (Chapter 8). We performed a matched-control study and found that the incidence of severe heterotopic ossification (Brooker grades 3 and 4) was lower in the patients treated with pulsed lavage (3% vs 17%). Our study had some design weaknesses however. We evaluated only radiographs, not patients' actual hip range of motion, and used historical controls, not randomized controls. On the other hand, pulsed lavage is cheap, quick and has no known adverse effects.

Future research should elucidate whether >36mm heads are clinically more stable than 32mm heads and what their revision rate is compared to 32mm heads. These data should be compiled for each bearing type (e.g. metal-on-polyethylene, ceramic-on-poly-ethylene, etc.). Given the low incidence of both dislocation and revision, this will require either a joint registry, or large numbers of patients followed long-term to obtain adequate power. A randomized clinical trial can elucidate whether pulsed lavage indeed prevents severe heterotopic ossification and affects range of motion clinically.

4. To study the effects of cobalt and chromium ions on osteoblast cells in-vitro.

We investigated the effects of cobalt and chromium ions on osteoblast cells in-vitro (Chapter 9). We used clinically relevant concentrations of 1, 10 and 100 µg/L, and assessed cytotoxicity (cell number and cellular activity), oxidative stress, and the influence on the expression of bone turnover regulatory proteins receptor activator of nuclear factor kappaB ligand (RANKL) and osteoprotegerin (OPG). We found that higher ion concentrations were more toxic for osteoblasts, especially in the first 24 hours. Chromium was more toxic than cobalt, but both ions combined yielded greatest cell reduction. Cell activity decreased when chromium ion concentration increased. Our results support available studies describing the detrimental influence of cobalt and chromium ions on osteoblasts.[31] It was not known however, whether RANKL and OPG were involved in the effects of cobalt and chromium ions on osteoblasts. RANKL and OPG regulate the interplay between osteoblasts and osteoclasts and are key factors in periprosthetic osteolysis.[32] Our results show reduced OPG to RANKL ratio's at 72 hours and beyond, indicating net bone loss starting from Co 10 µg/L, Cr 1 µg/L and Co+Cr 1 µg/L. For clinical practice, this suggests that even in well functioning metal-on-metal implants with systemic cobalt and chromium levels around 1 µg/L, local periprosthetic osteolytic reactions may be expected. The oxidative stress response visible after 96 hours further strengthens this assumption. On the other hand, high ion concentrations were not more osteolytic than low concentrations based on the OPG to RANKL ratios. We have excluded lymphocytes in our experiment. Lymphocytes can also lead to RANKL activation[33] and have been retrieved in periprosthetic tissues from metal-on-metal arthroplasties and implicated in ALVAL.[10] It is possible that lymphocyte-mediated RANKL activation is dose-dependent on cobalt and chromium ion levels. Most certainly, in clinical practice the effects of lymphocytes on RANKL are added to the effects of osteoblasts on RANKL, strengthening the total effect.

In conclusion, the main findings of our in-vitro study are that cobalt and chromium ions, in clinically relevant concentrations, reduce human osteoblast activity, reduce the OPG to RANKL ratio suggesting osteolysis, and lead to oxidative stress.

Future research should further elucidate the influence of lymphocytes on RANKL and OPG and their role in metal-on-metal prosthetic failure. RANKL and OPG could be measured in so-called pseudotumors. The value of RANKL-inhibitors and Vitamine-C for preventing periprosthetic osteolysis in metal-on-metal bearings could be addressed.

CONCLUSIONS

Based on the results from this thesis, I conclude:

1. Cemented 28mm metal-on-metal THA is clinically not better, nor worse than cemented 28mm metal-on-polyethylene THA, at 5 and 10 years follow-up. Metal-on-metal THA induces elevated serum cobalt and chromium ion levels. These elevated levels do not necessarily lead to clinical consequences, but carry potential biological risks.
2. Cementless large femoral head metal-on-metal THA is clinically comparable to cementless 28mm metal-on-polyethylene THA, at 1 year follow-up. The large femoral head metal-on-metal THA can however preserve periprosthetic acetabular bone density.
3. Large femoral head THA has no clinically relevant benefits over 28mm THA in terms of range of motion. Peroperative pulsed lavage can prevent severe heterotopic ossifications after cementless THA.
4. Cobalt and chromium ions, in clinically relevant concentrations, reduce osteoblast activity in-vitro, lead to oxidative stress and alter the balance between receptor activator of nuclear factor kappaB ligand and osteoprotegerin consistent with osteolysis.

REFERENCES

1. Van der Schaaf DB, Deutman R, Mulder TJ. Stanmore total hip replacement: a nine- to ten-year follow-up. J Bone Joint Surg 1988, 70B:45-48.
2. Alsema R, Deutman R, Mulder TJ. Stanmore total hip replacement. A 15- to 16-year clinical and radiographic follow-up. J Bone Joint Surg 1994, 76B:240-244.
3. Gerritsma-Bleeker CL, Deutman R, Mulder TJ, Steinberg JD. The Stanmore total hip replacement. A 22-year follow-up. J Bone Joint Surg 2000, 82B:97-102.
4. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. J Bone Joint Surg 2000, 82A:789-798.
5. Levai JP, Descamps S, Roch G, Boisgard S. Early aseptic loosening of cemented cup in metal-on-metal total hip arthroplasties [Article in French]. Rev Chir Orthop Reparatrice Appar Mot 2006, 92:575-580.
6. Eswaramoorthy V, Moonot P, Kalairajah Y, Biant LC, Field RE. The Metasul metal-on-metal articulation in primary total hip replacement. Clinical and radiological results at ten years. J Bone Joint Surg 2008, 90B:1278-1283.
7. Lazennec JY, Boyer P, Poupon J, Rousseau MA, Roy C, Ravaud P, Catonné Y. Outcome and serum ion determination up to 11 years after implantation of a cemented metal-on-metal hip. Acta Orthop 2009, 80:168-173.
8. Randelli F, Banci L, D'Anna A, Visenti O, Randelli G. Cementless Metasul metal-on-metal total hip arthroplasties at 13 years. J Arthroplasty 2011 May 31 [Epub ahead of print].
9. AOA. Australian Orthopaedic Association National Joint Replacement Registry, Annual report. Adelaide: AOA, 2010.
10. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Köster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg 2005, 87A:28-36.
11. Qu X, Huang X, Dai K. Metal-on-metal or metal-on-polyethylene for total hip arthroplasty: a meta-analysis of prospective randomized studies. Arch Orthop Trauma Surg 2011 Jun 4 [Epub ahead of print].
12. Laursen MB, Nielsen PT, Søballe K: Detection of bony defects around cementless acetabular components in total hip arthroplasty: a DEXA study on 10 human cadavers. Acta Orthop 2006, 77(2): 209-217.
13. Kim YH, Yoon SH, Kim JS: Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement. Alumina-on-alumina versus alumina-on-polyethylene articulation. J Bone Joint Surg Br 2007, 89-B:174-179.
14. Bolland BJRF, Culliford DJ, Langton DJ, Millington JPS, Arden NK, Latham JM. High failure rates with a large-diameter hybrid metal-on-metal total hip replacement: clinical, radiological and retrieval analysis. J Bone Joint Surg Br 2011 93:608-615.
15. Lavigne M, Belzille EL, Roy A, Morin F, Amzica T, Vendittoli PA. Comparison of whole-blood metal ion levels in four types of metal-on-metal large-diameter femoral head total hip arthroplasty: the potential influence of the adaptor sleeve. J Bone Joint Surg Am 2011, 93 Suppl 2:128-136.
16. Mistry A, Cahir J, Donell ST, Nolan J, Toms AP. MRI of asymptomatic patients with metal-on-metal and polyethylene-on-metal total hip arthroplasties. Clin Radiol 2011, 66:540-545.
17. Dumbleton JH, Manley MT: Metal-on-metal total hip arthroplasty: what does the literature say? J Arthroplasty 2005, 20(2):174-188.
18. Grübl A, Marker M, Brodner W, Giurea A, Heinze G, Meisinger V, Zehetgruber H, Kotz R: Long-term follow-up of metal-on-metal total hip replacement. J Orthop Res 2007, 25(7):841-848.
19. Zijlstra WP, Van Raay JJAM, Bulstra SK, Deutman R: No superiority of cemented metal-on-metal over metal-on-polyethylene total hip arthroplasty in a randomized controlled trial at 10 years follow-up. Orthopedics 2010, 33:154-161.
20. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, Gill HS: Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg (Am) 2008, 90-A:202-208.

21. Haddad FS, Thakrar RR, Hart AJ, Skinner JA, Nargol AVF, Nolan JF, Gill HA, Murray DW, Blom AW, Case CP. Metal-on-metal bearings: the evidence so far. J Bone Joint Surg Br 2011, 93B: 572-579.
22. NOV. Advies metaal op metaal articulerende implantaten (MOM). ‘s Hertogenbosch: Nederlandse Orthopaedische Vereniging, 9 June 2011.
23. AAHKS. Information for our patients regarding metal-on-metal (MoM) hip replacements. The American Association of Hip and Knee Surgeons, the Hip Society, the American Academy of Orthopaedic Surgeons, 5 February 2011.
24. AOA Working Group. Update on metal-on-metal prostheses. Sydney: Australian Orthopaedic Association, 19 April 2011.
25. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR. Biomechanics of large femoral heads: what they do and don’t do. Clin Orthop Relat Res 2004, 429:102-107
26. Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH. Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 2005, 20(1):11-19
27. Lavigne M, Ganapathi M, Mottard S, Girard J, Vendittoli PA. Range of motion of large head total hip arthroplasty is greater than 28mm total hip arthroplasty or hip resurfacing. Clin Biomech 2010, doi:10.1016/j.clinbiomech.2010.11.001
28. NOV. Richtlijn totale heup prothese. ‘s Hertogenbosch: Nederlandse Orthopaedische Vereniging, 2010.
29. Cinotti G, Lucioli N, Malagoli A, Calderoli C, Cassese F. Do large femoral heads reduce the risks of impingement in total hip arthroplasty with optimal and non-optimal cup positioning? Int Orthop 2010, 35:317-323.
30. Medley JB. Tribology of bearing materials. In: Amstutz HC, ed. Hip resurfacing: principles, indications, technique and results. Philadelphia: Saunders Elsevier, 2008:33-38.
31. Mabilleau, G, Kwon, YM, Pandit, H, et al. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. Acta Orthop 2008, 79: 734-747.
32. Robling, A, Castillo, A, Turner, C. Biomechanical and molecular regulation of bone remodeling. Annual Review of Biomedical Engineering 2006, 8: 455-498.
33. Purdue, PE, Koulouvaris, P, Nestor, BJ, Sculco, TP. The central role of wear debris in periprosthetic osteolysis. HSS J 2006, 2: 102-113.

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Tanna, Vanuatu

Summary & samenvatting

Men moat net alles sizze wat men wit, mar wòl alles witte wat men seit

Men moet niet alles zeggen wat men weet, maar wèl alles weten wat men zegt

SUMMARY

Total hip arthroplasty (THA) is a very successful treatment for alleviating end-stage osteoarthritis of the hip. The rate of hip replacement surgery is increasing worldwide. Initially designed for elderly patients with crippling osteoarthritis, the procedure is now performed in young patients hoping to regain quality of life and physically demanding activities. With these young patients in mind, so-called alternative bearing materials were designed, for example ceramic-on-ceramic and metal-on-metal. These alternative bearings aim to increase the longevity of the prosthesis by reducing wear debris, osteolysis and aseptic loosening.

This thesis focuses on one of the alternative bearings above, namely metal-on-metal total hip arthroplasty. General aim of this thesis is **to determine the clinical outcome and bone implications of metal-on-metal total hip arthroplasty. We formulated four research objectives.**

1. To determine the mid and long term clinical outcome of cemented 28mm metal-on-metal THA in comparison with metal-on-polyethylene THA

We studied the clinical outcome of a cemented 28mm metal-on-metal THA. We performed a prospective randomized trial and used a cemented 28mm metal-on-polyethylene THA as a comparison. We found that both prostheses led to significant clinical improvements. At both 5-year (Chapter 3) and 10-year follow-up (Chapter 4), the clinical results did not differ between the two groups, nor did the radiological results. Five-year prosthetic survival was 97% for the metal-on-metal articulation and 99% for the metal-on-polyethylene articulation, with no significant difference. Ten-year survival was 96% and 97% respectively, with no statistically significant difference. Ten-year median serum cobalt and chromium ion levels were higher in the metal-on-metal group (1.1 resp. 1.0 µg/L, versus 0.5 resp. 0.5 µg/L).

Our clinical results and survival are comparable to, or even better than other cemented metal-on-metal THA series. Based on clinical results, radiological performance and prosthetic survival, the cemented 28mm metal-on-metal THA in our series performed well. We did not find any specific metal-on-metal bearing related adverse events, apart from one patient. To the existing literature, our study has added the only published randomized trial on metal-on-metal THA with 10 years follow-up.

2. To determine the short term clinical outcome and periprosthetic bone implications of cementless large femoral head metal-on-metal THA in comparison with metal-on-polyethylene THA

We designed a randomized clinical trial to assess clinical outcome and periprosthetic bone density changes around the acetabular component of a cementless large femoral head metal-on-metal THA (Chapter 5). We used a cementless 28mm metal-on-polyethylene THA as a comparison. At one year postoperatively, the clinical results were comparable. We further found retained acetabular bone density with the large head metal-on-metal THA (Chapter 6). Bone density had decreased over the year in 3 of 4 regions of interest in the metal-on-polyethylene patients, but was retained in all regions in the metal-on-metal patients. Bone density preservation was most pronounced superior to the cup. Although a follow-up of one year is very short, the finding of preservation of acetabular bone with a large head hard-on-hard bearing is novel, as far as we know. It will be essential to see what happens to the acetabular bone density after 5 or 10 years, when the effects of metal wear particles and ions start to take effect.

Bone density was not related to serum metal ion levels, in spite of elevated cobalt and chromium levels with the metal-on-metal bearings (1.7, resp. 2.1 μg/L). The ion levels were in line with the literature and maximum values were less than those mentioned as a risk for metallosis. A major task for future research is to establish predictive cut-offs for cobalt and chromium ion levels indicating possible future prosthetic failure.

3. To assess the effect of large femoral head THA on range of motion and to study heterotopic ossification as a factor that can compromise range of motion

We studied clinical range of motion (ROM) after large femoral head metal-on-metal THA (Chapter 7). Again, we used a 28mm metal-on-polyethylene THA for comparison, in a randomized trial. Hip simulator and biomechanical studies suggest that large femoral heads can prevent dislocation and lead to greater ROM, but the latter had not been shown clinically so far. We found that improvement in endorotation was greater after large (48mm) femoral head total hip arthroplasty, compared to 28mm THA (14 versus 7°). However, no differences in absolute postoperative endorotation or other ROM measures (flexion, extension, abduction or adduction) were found. Whether this small difference in endorotation improvement (7°) is clinically relevant is open to discussion. We estimate our measurement error to be around 4° based on our clinical method of ROM measurements.

Severe heterotopic ossifications (HO) may compromise hip range of motion. We studied the incidence of HO after cementless THA, with and without peroperative pulsed lavage (Chapter 8). We performed a matched-control study and found that the incidence of severe heterotopic ossification was lower in the patients treated with pulsed lavage (3% vs 17%).

4. To study the effects of cobalt and chromium ions on osteoblast cells in-vitro.

We investigated the effects of cobalt and chromium ions on osteoblast cells in-vitro (Chapter 9). We used clinically relevant concentrations of 1, 10 and 100 µg/L, and assessed cytotoxicity (cell number and cellular activity), oxidative stress, and the influence on the expression of bone turnover regulatory proteins receptor activator of nuclear factor kappaB ligand (RANKL) and osteoprotegerin (OPG). We found that higher ion concentrations were more toxic for osteoblasts, especially in the first 24 hours. Chromium was more toxic than cobalt, but both ions combined yielded greatest cell reduction. Cell activity decreased when chromium ion concentration increased.

Our results support available studies describing the detrimental influence of cobalt and chromium ions on osteoblasts. It was not known however, whether RANKL and OPG were involved in the effects of cobalt and chromium ions on osteoblasts. RANKL and OPG regulate the interplay between osteoblasts and osteoclasts and are key factors in periprosthetic osteolysis. Our results show reduced OPG to RANKL ratio's at 72 hours and beyond, indicating net bone loss starting from Co 10 µg/L, Cr 1 µg/L and Co+Cr 1 µg/L. The oxidative stress response visible after 96 hours further strengthens these findings. On the other hand, high ion concentrations were not more osteolytic than low concentrations based on the OPG to RANKL ratios.

In conclusion, the main findings of our in-vitro study are that cobalt and chromium ions, in clinically relevant concentrations, reduce human osteoblast activity, lead to oxidative stress and reduce the OPG to RANKL ratio suggesting osteolysis. For clinical practice, this suggests that even in well functioning metal-on-metal implants local periprosthetic osteolytic reactions may be expected.

CONCLUSIONS

1. Cemented 28mm metal-on-metal THA is clinically not better, nor worse than cemented 28mm metal-on-polyethylene THA, at 5 and 10 years follow-up. Metal-on-metal THA induces elevated serum cobalt and chromium ion levels. These elevated levels do not necessarily lead to clinical consequences, but carry potential biological risks.
2. Cementless large femoral head metal-on-metal THA is clinically comparable to cementless 28mm metal-on-polyethylene THA, at 1 year follow-up. The large femoral head metal-on-metal THA can however preserve periprosthetic acetabular bone density.
3. Large femoral head THA has no clinically relevant benefits over 28mm THA in terms of range of motion. Peroperative pulsed lavage can prevent severe heterotopic ossifications after cementless THA.
4. Cobalt and chromium ions, in clinically relevant concentrations, reduce osteoblast activity in-vitro, lead to oxidative stress and alter the balance between receptor activator of nuclear factor kappaB ligand and osteoprotegerin consistent with osteolysis.

SAMENVATTING

De totale heup prothese (THA) is een succesvolle behandeling voor het verlichten van ernstige artrose van het heupgewricht. Het aantal totale heup vervangingen neemt wereldwijd toe. In eerste instantie werd de totale heup prothese alleen geplaatst bij invaliderende artrose van de heup, maar tegenwoordig wordt de procedure verricht bij jonge patiënten ter verbetering van de kwaliteit van leven en ten behoeve van fysiek veeleisende activiteiten. Voor deze jonge actieve patiënten zijn alternatieve articulaties ontwikkeld, zoals keramiek op keramiek, en metaal op metaal. Deze alternatieve articulaties hebben als doel de levensduur van de prothese te verlengen door het verminderen van slijtage partikels, osteolyse en aseptische loslating.

Dit proefschrift richt zich op één van deze alternatieve articulaties, namelijk de metaal op metaal totale heup prothese. De hoofddoelstelling is **het bepalen van de klinische uitkomst en de bot implicaties van de metaal op metaal totale heup prothese.** Er zijn vier onderzoeksdoelen. Per doel worden de belangrijkste onderzoeksresultaten besproken.

1. Het bepalen van de midden- en lange-termijn klinische resultaten van een gecementeerde 28mm metaal op metaal THA, vergeleken met een 28mm metaal op polyethyleen THA.

Wij bestudeerden de klinische uitkomst van een gecementeerde 28mm metaal op metaal THA. We verrichtten een prospectieve gerandomiseerde studie en gebruikten een gecementeerde 28mm metaal op polyethyleen THA als vergelijking. We vonden dat beide protheses leidden tot significante klinische verbeteringen. Na 5 jaar (Hoofdstuk 3) en na 10 jaar (Hoofdstuk 4) was er geen verschil tussen beide prothese groepen wat betreft de klinische en radiologische resultaten. De overleving van de prothese was na 5 jaar 97% voor de metaal op metaal groep en 99% voor de metaal op polyethyleen groep. Dit verschil was statistisch niet significant. Na 10 jaar lagen deze getallen respectievelijk op 96% en 97%, wederom zonder significant verschil. De mediane cobalt en chroom ion concentraties in het serum waren hoger bij de metaal op metaal patiënten (1,1 respectievelijk 1,0 versus 0,5 en 0,5 µg/L).

Onze klinische resultaten en overleving van de metaal op metaal prothese zijn vergelijkbaar met of zelfs beter dan andere gecementeerde metaal op metaal totale heup protheses. Wij vonden geen specifieke metaal op metaal gerelateerde neven effecten, op één patiënt na. Onze studie is de enige gepubliceerde gerandomiseerde studie naar een metaal op metaal THA met 10 jaar follow-up.

2. Het bepalen van de korte termijn klinische resultaten en botdichtheidsveranderingen van een ongecementeerde metaal op metaal THA met grote femurkop, vergeleken met een 28mm metaal op polyethyleen THA.

We ontwierpen een gerandomiseerde klinische studie om de klinische uitkomst en de botdichtheidsveranderingen rond de cup te meten van een cementloze metaal op metaal THA met grote femurkop (Hoofdstuk 5). We gebruikten een cementloze 28mm metaal op polyethyleen THA als vergelijking. Na 1 jaar waren de klinische resultaten van beide protheses vergelijkbaar. Verder vonden we dat er behoud van botdichtheid was rond de cup van de metaal op metaal THA met grote kop (Hoofdstuk 6). Na 1 jaar was de botdichtheid afgenomen in 3 van de 4 regio's rond de metaal op polyethyleen cup; de botdichtheid was echter stabiel gebleven rond de metaal op metaal cup. Vooral boven de cup was dit zichtbaar. Hoewel de follow-up van 1 jaar erg kort is, is de bevinding van botbehoud rond een hard op hard articulatie met grote kop nieuw. Het is belangrijk om te volgen wat er met het acetabulaire bot gebeurt na 5 en 10 jaar, wanneer de effecten van metaal partikels en ionen merkbaar worden.

Botdichtheid bleek niet gerelateerd aan serum metaal ion concentraties, ondanks verhoogde cobalt en chroom ion spiegels bij de metaal op metaal patiënten (1,7 respectievelijk 2,1 µg/L). De ion spiegels kwamen overeen met de literatuur en de hoogste waarden waren lager dan de metallose risico waardes. Een grote uitdaging voor toekomstig onderzoek is het vaststellen van voorspellende grenswaarden voor chroom en cobalt spiegels met betrekking tot toekomstig falen van metaal op metaal protheses.

3. Het bepalen van het effect van een grote femurkop op de klinische beweeglijkheid van de heup, en het bestuderen van heterotope ossificatie als factor die deze beweeglijkheid kan belemmeren.

Wij bestudeerden de klinische beweeglijkheid van de heup na een metaal op metaal THA met grote femurkop (Hoofdstuk 7). Opnieuw gebruikten we een 28mm metaal op polyethyleen THA als vergelijk, binnen een gerandomiseerde studie. Uit heup simulator en biomechanische studies bleek dat grote femukoppen heupluxaties kunnen voorkomen en de beweeglijkheid van het heupgewricht kunnen vergroten. Dit laatste was echter nog niet aangetoond in de kliniek. Wij vonden dat de winst in endorotatie groter was na een THA met grote femurkop (gemiddeld 48mm), vergeleken met een 28mm femurkop (14 versus 7 graden). De absolute postoperatieve endorotatie verschilde echter niet significant. Dit gold ook voor flexie, extensie, abductie en adductie. Of dit kleine verschil (7 graden) in endorotatie verbetering klinisch relevant is, is open voor discussie. We schatten onze meetfout op ongeveer 4 graden, gebaseerd op onze klinische meetmethode.

Ernstige heterotope ossificaties kunnen de beweeglijkheid van de heup belemmeren. Wij onderzochten de incidentie van heterotope ossificaties na cementloze THA, met en zonder peroperatieve puls lavage (Hoofdstuk 8). We verrichtten een matched-control studie en vonden dat de incidentie van ernstige heterotope ossificaties lager was na het gebruik van puls lavage (3% versus 17%).

4. Het bestuderen van het effect van cobalt en chroom ionen op humane osteoblasten in-vitro.

Wij onderzochten de effecten van cobalt en chroom ionen op osteoblast cellen in-vitro (Hoofdstuk 9). We gebruikten klinisch relevante concentraties van 1, 10 en 100 µg/L en bepaalden cytotoxiciteit (cel aantal en cel activiteit), oxidatieve stress en de expressie van receptor activator of nuclear factor kappaB ligand (RANKL) en osteoprotegerin (OPG), twee stoffen die de botaanmaak en botafbraak sturen. We vonden dat hogere ion concentraties toxischer waren voor osteoblasten, vooral in de eerste 24 uur. Chroom was meer toxisch dan cobalt, maar beide ionen gecombineerd resulteerde in de sterkste cel reductie. De cel activiteit nam af wanneer de chroom concentratie toenam.

Onze resultaten bevestigen de eerder beschreven negatieve invloed van cobalt en chroom ionen op osteoblasten. Tot op heden was echter niet bekend of RANKL en OPG hierin een rol speelden. RANKL en OPG reguleren de interactie tussen osteoblasten en osteoclasten en spelen een cruciale rol in periprothetische osteolyse. Onze resultaten laten verlaagde OPG / RANKL ratio's zien vanaf 72 uur incubatietijd, pleitend voor netto botverlies vanaf 10 µg/L cobalt, 1 µg/L chroom en 1 µg/L chroom+cobalt. De oxidatieve stress respons die we zagen na 96 uur, versterkt dit. Aan de andere kant waren hoge ion concentraties niet méér osteolytisch dan lage ion concentraties, gebaseerd op de OPG / RANKL ratio's.

Concluderend zijn de belangrijkste resultaten van de in-vitro studie dat cobalt en chroom ionen, in klinisch relevante concentraties, de activiteit van humane osteoblasten reduceren, leiden tot oxidatieve stress en de balans tussen OPG en RANKL beïnvloeden, wijzend op osteolyse. Voor de klinische praktijk betekent dit dat zelfs rond klinisch goed functionerende metaal op metaal protheses er lokale periprothetische osteolyse verwacht kan worden.

CONCLUSIES

1. Na 5 en 10 jaar follow-up is een gecementeerde 28mm metaal op metaal totale heup prothese klinisch niet beter, maar ook niet slechter dan een gecementeerde 28mm metaal op polyethyleen totale heup prothese. Een metaal op metaal totale heup prothese leidt tot verhoogde serum cobalt en chroom ionen spiegels. Deze verhoogde spiegels leiden niet noodzakelijkerwijs tot klinische gevolgen, maar hebben potentiële biologische risico's.
2. Een ongecementeerde metaal op metaal totale heup prosthese met een grote kop is, na 1 jaar, klinisch vergelijkbaar met een ongecementeerde 28mm metaal op polyethyleen prothese. De metaal op metaal prothese behoudt daarentegen na 1 jaar het periprothetische bot in het acetabulum beter.
3. Een totale heup prothese met grote kop (48mm) heeft - voor wat betreft de post-operatieve beweeglijkheid van de heup - geen klinisch relevante voordelen ten opzichte van een prothese met 28mm kop. Peroperatieve pulslavage vermindert ernstige heterotope ossificaties na een ongecementeerde totale heup prothese.
4. Cobalt en chroom ionen, in klinisch relevante concentraties, verminderen de activiteit van osteoblasten in-vitro en leiden tot oxidatieve stress. Daarnaast veranderen ze de balans tussen receptor activator of nuclear factor kappaB ligand (RANKL) en osteoprotegerin (OPG), passend bij osteolyse.

Al met al is de metaal op metaal totale heup prothese niet beter gebleken dan de metaal op polyethyleen prothese. De vrijkomende cobalt en chroom ionen hebben negatieve effecten op osteoblasten. Het gebruik van een ongecementeerde hard op hard articulatie met grote femurkop biedt daarentegen mogelijk wel voordelen, bijvoorbeeld in de vorm van minder botverlies rond de cup.

Addendum

Carthagena, Colombia

Ien stien allinne makket gjin moal
Een steen alleen maalt geen meel

DANKWOORD

Promotor prof.dr. S.K. Bulstra, beste Sjoerd. Er zijn weinig professoren die zo down-to-earth zijn als jij. Je bent makkelijk aanspreekbaar en geeft mensen de creatieve en emotionele ruimte om zelf verantwoordelijkheid te nemen voor zowel onderzoek als kliniek. Dat is volgens mij je grootste kracht. Het heeft mij in ieder geval gestimuleerd en het is een eer en een genot om onder je te promoveren. Daarnaast hoop ik dat mijn meiden nog lang je befaamde koekjes mogen blijven proeven. En wij een biertje.

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PUBLICATIES EN PRESENTATIES

Publicaties

Zijlstra WP, Bulstra SK, Van Raay JJAM, MBM van Leeuwen, Kuijer R. Cobalt and chromium ions reduce human osteoblast-like cell activity in-vitro, reduce the OPG to RANKL ratio and induce oxidative stress. J Orthop Res, conditionally accepted.

Zijlstra WP, Van der Veen HC, Van den Akker-Scheek I, Zee MJM, Bulstra SK, Van Raay JJAM. Retained periprosthetic acetabular bone density after large femoral head metal-on-metal total hip arthroplasty: short-term results of a randomized trial. Submitted.

Mellema JJ, Zijlstra WP, Ten Have BLEF, Van Raaij TM, Van Raay JJAM. Pulsed lavage in cementless total hip arthroplasty reduces the incidence of Brooker grade 3 and 4 heterotopic ossifications. Submitted.

Zijlstra WP, Van den Akker-Scheek I, Zee MJM, Van Raay JJAM. No clinical difference between large metal-on-metal total hip arthroplasty and 28mm head total hip arthroplasty? Int Orthop 2011 Mar 4.

Zijlstra WP, Van Raay JJ, Bulstra SK, Deutman R. No Superiority of Cemented Metal-on-Metal Over Metal-on-Polyethylene THA in a Randomized Controlled Trial at 10-Year Follow-up. Orthopedics 2010; 33:154-161.

Zijlstra WP, Cheung C, Sietsma MS, Van Raay JJAM, Deutman R. No superiority of cemented metal-on-metal over metal-on-polyethylene total hip arthroplasty in a randomized controlled trial at 5 years follow-up. Orthopedics 2009; 32:479.

Zijlstra WP, Bos N, van Raaij JJ. Large head metal-on-metal cementless total hip arthroplasty versus 28 mm metal-on-polyethylene cementless total hip arthroplasty: design of a randomized controlled trial. BMC Musculoskelet Disord 2008 Oct 8:9:136.

Giannoudis PV, Pape HC, Bulstra SK, Zijlstra WP. Practical procedures in orthopaedic trauma surgery. Ned Tijdschr Geneesk 2008;152:1703.

Mercier LR, Bulstra SK, Zijlstra WP. Practical orthopedics. Ned Tijdschr Geneesk 2008;152:2826.

Zijlstra WP, van Raay JJAM. Een 65-jarige patiënte met een densfractuur veroorzaakt door headbangen. Ned Tijdschr Geneesk 2008;152:1743-5.

Kuiken DS, Zijlstra WP, van Raay JJAM. Geïsoleerde ruptuur van het ligamentum deltoideum. Ned Tijdschr Traumatol 2006; 5 (Okt):129.

Onderwater JPAH, Zijlstra WP, van Raay JJAM. Een gezwollen kuit na arthroscopie van de knie. Ned Tijdschr Orthop 2006; 2 (Jun):124-126.

Bisschop R, de Leeuw LA, Zijlstra WP, van der Velde D. Midschacht claviculafracturen: altijd conservatief? Retrospectieve studie naar de resultaten van conservatieve therapie. Ned Tijdschr Traumatol 2005; 3:72-76.

Zijlstra WP, Driessen APPM, Kraai M, van Horn JR. Een patiënt met multipele osteochondrosen. Ned Tijdschr Orthop 2002/2003, overgangseditie, p.15-18.

Presentaties

Zijlstra WP, Van der Veen HC, Van den Akker-Scheek I, Zee MJM, Bulstra SK, Van Raay JJAM. Behoud van periprosthetische acetabulaire botdichtheid na metal-on-metal totale heup arthroplastiek met grote femurkop: korte termijnsresultaten van een gerandomiseerde trial. Mondelinge presentatie NOV Najaarsvergadering, Noordwijkerhout, 6 oktober 2011.

Zijlstra WP, Sietsma MS, Van Raay JJAM, Bulstra SK, Deutman R. No Superiority of Cemented Metal-on-Metal Over Metal-on-Polyethylene THA in a Randomized Controlled Trial at 10-Year Follow-up. Mondelinge presentatie en prijswinnaar Van Swieten Wetenschapsprijs, Groningen, 8 februari 2011.

Zijlstra WP, van Raay JJAM, Bulstra SK, Deutman R. Gecementeerde metal-on-metal versus metal-on-polyethylene totale heup arthroplastiek: 10-jaars resultaten van een gerandomiseerde klinische trial. Mondelinge presentatie NOV Jaarcongres ‘Heupchirurgie’, Utrecht, 21 januari 2010. Genomineerd voor de NOV Orthomed-prijs. Abstract in Ned Tijdschr Orthop 2010; 1 (Mrt).

Zijlstra WP, Gerritsma-Bleeker CLE, van den Akker-Scheek I, van Raay JJAM. Beweeglijkheid van de heup 1 jaar postoperatief: Resurfacing HA versus metal-on-metal THA versus metal-on-polyethylene THA. Een gerandomiseerde en parallele groep studie. Mondelinge presentatie NOV Jaarcongres ‘Heupchirurgie’, Utrecht, 21 januari 2010. Abstract in Ned Tijdschr Orthop 2010; 1 (Mrt).

Zijlstra WP, Gerritsma-Bleeker CLE, van den Akker-Scheek I, van Raay JJAM. Metal-polyethylene THA vs. metal-metal THA vs. metal-metal heup resurfacing. Vroege serum cobalt en chroom ion concentraties in een gerandomiseerde en parallele groep studie. Mondelinge presentatie NOV Voorjaarsvergadering, Utrecht, 15 mei 2009. Abstract in Ned Tijdschr Orthop 2009; 2 (Jun): 83-84.

Zijlstra WP, Gerritsma-Bleeker CLE, van den Akker-Scheek I, van Raay JJAM. Large head metal-on-metal total hip arthroplasty versus 28mm metal-on-polyethylene hip arthroplasty versus metal-on-metal hip resurfacing: early serum cobalt and chromium ion levels in a randomized and parallel group trial. Poster presented at the 2nd Annual US Comprehensive Course on Total Hip Resurfacing Arthroplasty in Los Angeles, USA, 24-25 Oct 2008.

Zijlstra WP, van Leeuwen BM, Kuijer R, Bulstra SK. Cobalt and chromium ions inhibit human osteoblast cells. Poster presented at the 2nd Annual US Comprehensive Course on Total Hip Resurfacing Arthroplasty in Los Angeles, USA, 24-25 Oct 2008.

Zijlstra WP, Cheung J, Sietsma MS, van Raaij JJAM, Deutman R. Cemented metal-on-metal versus metal-on-polyethylene total hip arthroplasty: equal results at 5 years follow-up in a prospective randomised trial. Oral presentation at the 54th Nordic Orthopaedic Federation Congress in Amsterdam, 12 June 2008.

Zijlstra WP, van Leeuwen MBM, Kuijer R, Bulstra SK. Cobalt and chromium ions inhibit human osteoblast cells. Poster presented at the 54th Nordic Orthopaedic Federation Congress in Amsterdam, 11-13 June 2008.

Zijlstra WP, MBM van Leeuwen, Kuijer R, Bulstra SK. Effects of cobalt and chromium ions on human osteoblast cells in vitro. Oral presentation at the European Cooperation in Science and Technology Meeting on 'Materials for improved wear resistance of total artificial joints' (COST 533) in Groningen, 26 May 2008.

Bruseker T, Zijlstra WP, van der Velde D. Vroege behandeling d.m.v. botgroeistimulatie lijkt tot snellere genezing te leiden bij delayed union. Mondelinge presentatie Assistenten Traumatologie Symposium, januari 2004.

Bisschop R, de Leeuw LA, Zijlstra WP, van der Velde D. Claviculafracturen: altijd conservatief? Mondelinge presentatie Assistenten Traumatologie Symposium, januari 2004.

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